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ENDOCRINOLOGY

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THE HIGH INCIDENCE OF HYPERTENSION IN TOXIC GOITER AND IN MYXEDEMA*

WILLARD OWEN THOMPSON, M.D., LOIS F. N. DICKIE, B.S., ALBERT E. MORRIS, M.D., AND B. H. HILKEVITCH, M.D.

From the Department of Medicine, Rush Medical College, and The Presbyterian Hospital

CHICAGO

and

The Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital

BOSTON

Observations of the blood pressure have been made in 149 cases of toxic goiter and in 24 cases of myxedema, before and after the basal metabolism had been restored to normal by appropriate treatment. These observations are summarized in Tables 1 and 2, and for comparison with them, the blood pressures in a series of cases of non-toxic goiter are recorded in Table 3. It may be noted that 70 (47 per cent) of the patients with toxic goiter had a systolic blood pressure of 140 or over and 53 (35.5 per cent) of 150 or over, after the basal metabolism had been restored to the standard normal level. Of the 84 patients who were 40 years of age and over, 44 (52 per cent) had systolic blood pressures of 150 and over under these circumstances. From the standpoint of prognosis, it may be seen from Tables 4 and 5, and Charts 1 and 2, that if the diastolic pressure is 100 or more before treatment is started, the systolic pressure will almost surely be 150 or higher when the metabolism is normal; and if the systolic pressure is 190 or more before treatment, it is highly probable that hypertension will be present after treatment. However, a diastolic pressure below 100 or a systolic pressure below 150 before treatment does not guarantee that a hypertension will not be present after treatment. In about forty-five per cent of all cases in which the diastolic pressure ranged from 70 to 99 before treatment, hypertension was present afterward; and in 10 cases the systolic pressure rose to above 150 mm. mercury only after the basal metabolism had been restored to normal.

Owing to the small number of cases no attempt has been made to differentiate between toxic adenoma and exophthalmic goiter; the latter pre-

*Read by title at the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, June 8, 1931.

TABLE I

SYSTOLIC BLOOD PRESSURE IN 149 CASES OF TOXIC GOITER AFTER THE BASAL METABOLISM HAD BEEN RESTORED TO NORMAL (31 males, 118 females).

Systolic Blood Pressure After Basal Metabolism Had Been Restored to Normal	Number of Cases in Age Group							Total Number of Cases
	10–19 Years	20–29 Years	30–39 Years	40–49 Years	50–59 Years	60–69 Years	70–79 Years	
Mm. Mercury								
80– 89	...	1	...	...	...	...	...	1
90– 99	...	...	...	...	...	...	...	...
100–109	...	...	...	2	1	...	...	3
110–119	1	3	8	2	1	...	...	15
120–129	2	8	6	9	4	...	...	29
130–139	3	6	8	8	5	1	...	31
140–149	...	3	7	2	5	...	...	17
150–159	1	2	2	6	3	1	...	15
160–169	1	...	...	6	2	...	1	10
170–179	...	...	2	3	1	1	...	7
180–189	...	...	...	3	4	1	...	8
190–199	...	...	...	3	1	1	...	5
200–209	...	1	...	...	1	...	...	2
210–219	...	...	...	...	...	...	...	...
220–229	...	...	...	1	2	1	...	4
230–239	...	...	...	...	1	...	...	1
240–249	...	...	...	...	...	...	...	...
250–259	...	...	...	...	...	...	...	...
260–269	...	...	...	1	...	...	...	1
Total number of cases	8	24	33	46	31	6	1	149

dominated. For the same reason no attempt has been made to classify the patients according to sex; the majority were females.

In 13 (54 per cent) of the 24 cases of myxedema the systolic blood pressure was 140 mm. mercury or over after treatment, and in 9 (37.5 per cent), 150 or over. In 9 (50 per cent) of the 18 patients who were 40 years of age or over the systolic pressure was 150 mm. mercury or over after the basal metabolism had been raised to the normal level. In 4 of 13

TABLE II

SYSTOLIC BLOOD PRESSURE IN 24 CASES OF MYXEDEMA AFTER THE BASAL METABOLISM HAD BEEN RESTORED TO NORMAL BY TREATMENT

Systolic Blood Pressure After Basal Metabolism Had Been Restored to Normal	Number of Cases in Age Group							Total Number of Cases
	10–19 Years	20–29 Years	30–39 Years	40–49 Years	50–59 Years	60–69 Years	70–79 Years	
Mm. Mercury								
80– 89	...	...	...	...	...	...	...	...
90– 99	...	...	...	...	...	...	...	...
100–109	...	...	...	...	...	...	...	...
110–119	...	1	1	...	...	...	...	2
120–129	...	1	...	1	1	...	...	3
130–139	...	1	1	3	1	...	...	6
140–149	...	1	...	2	1	...	...	4
150–159	...	...	...	1	1	1	...	3
160–169	...	...	...	...	...	...	...	0
170–179	...	...	...	1	1	...	...	2
180–189	...	...	...	...	2	...	...	2
190–199	...	...	...	...	...	...	...	0
200–209	...	...	...	...	1	...	...	1
210–219	...	...	...	...	...	...	...	0
220–229	...	...	...	...	...	...	...	0
230–239	...	...	...	...	1	...	...	1
240–249	...	...	...	...	...	...	...	...
250–259	...	...	...	...	...	...	...	...
260–269	...	...	...	...	...	...	...	...
Total number of cases	...	4	2	8	9	1	...	24

TABLE III

SYSTOLIC BLOOD PRESSURE IN 53 CASES OF NON-TOXIC GOITER

Systolic Blood Pressure	Number of Cases in Age Group							Total Number of Cases
	10–19 Years	20–29 Years	30–39 Years	40–49 Years	50–59 Years	60–69 Years	70–79 Years	
Mm. Mercury								
80– 89	...	...	...	...	...	...	...	...
90– 99	2	2	...	...	...	...	...	4
100–109	...	2	4	...	...	...	...	6
110–119	2	3	9	1	...	...	...	15
120–129	4	...	5	1	2	...	...	12
130–139	2	2	4	1	1	...	...	10
140–149	...	...	...	5	...	...	...	5
150–159	...	...	...	...	...	...	...	0
160–169	...	...	...	1	...	...	...	1
Total number of cases	10	9	22	9	3	...	...	53

TABLE IV

RELATION BETWEEN INITIAL DIASTOLIC PRESSURE AND THE PRESENCE OF HYPERTENSION AFTER TREATMENT IN CASES OF TOXIC GOITER.

Initial Diastolic Pressure	Number of Cases	Number of Such Cases With Systolic Pressure 150 or Over After Treatment	Percentage With Hypertension After Treatment
Mm. Mercury			
40–49	3	0	0.0
50–59	7	0	0.0
60–69	27	5	18.5
70–79	26	11	42.3
80–89	43	19	44.2
90–99	10	5	50.0
100 or over	11	11	100.0

TABLE V

RELATION BETWEEN INITIAL SYSTOLIC PRESSURE AND THE PRESENCE OF HYPERTENSION AFTER TREATMENT IN CASES OF TOXIC GOITER.

Initial Systolic Pressure	Number of Cases	Number of Such Cases With Systolic Pressure 150 or Over After Treatment	Percentage With Hypertension After Treatment
Mm. Mercury			
Under 130	19	0	0.0
130–139	24	4	16.6
140–149	24	6	25.0
150–159	17	10	58.8
160–169	14	9	64.3
170–179	14	10	71.4
180 and over	15	12	80.0

cases in which measurements were made before and after treatment, the pressure rose to an abnormal level only when the basal metabolism became normal. The data, though small in number, suggest that just as in the cases of toxic goiter, a diastolic pressure of 100 or more before treatment is practically proof that hypertension is present in addition to the myxedema.

In comparison with the cases of toxic goiter and myxedema, only 1 of 12 patients with non-toxic goiter who were 40 years of age or more had a systolic blood pressure as high as 150 (Chart 3). The number of cases is

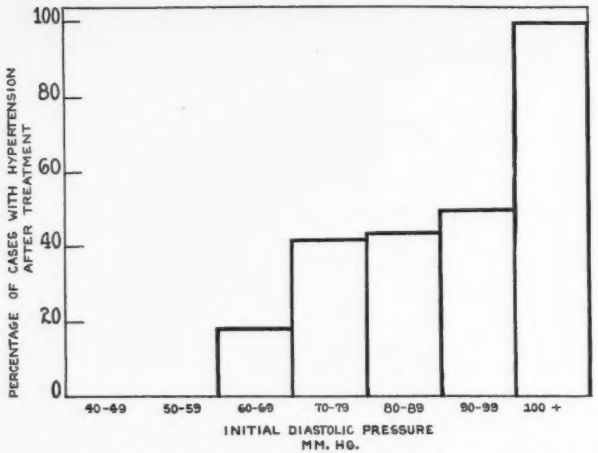

Chart 1. Relation between the initial diastolic pressure and the incidence of hypertension after treatment in cases of toxic goiter.

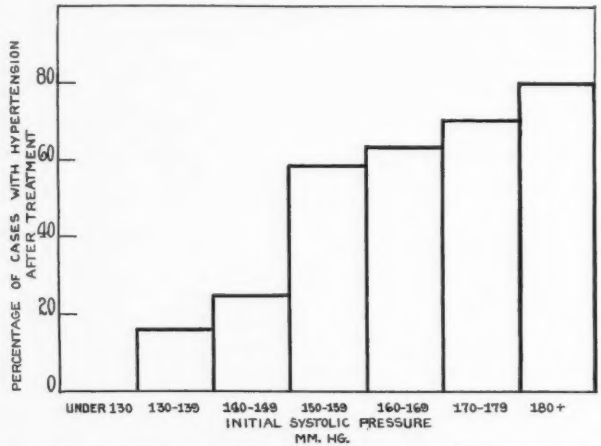

Chart 2. Relation between the initial systolic pressure and the incidence of hypertension after treatment in cases of toxic goiter.

too small to be very significant and the average age of the patients over 40 is less than in the other two groups. The difference is suggestive, nevertheless.

No attempt has been made to classify our cases of hypertension on the basis of etiology. It may be said, however, that clinical examination showed no evidence of renal impairment in the great majority.

DISCUSSION

Most of the blood pressure readings previously reported in cases of toxic goiter were made only during the period of thyrotoxicosis. The conclusions about the incidence of hypertension are variable. Most recent ob-

servations have dealt with variations in the pulse pressure. The most complete report on the subject appears to be that of Hurxthal (1), who found that 18 per cent of all his subjects had a systolic pressure of 150 or over, that the incidence was much greater in toxic adenoma than in exophthalmic goiter, and greater in severe cases of exophthalmic goiter than in mild ones. The incidence, of course, increased with the age. However, by comparing his average figures with those of normal control, patients with non-toxic goiter, office patients of Alvarez, and diabetic patients of Joslin, he came to the conclusion that the incidence of hypertension in toxic goiter was no greater than in the general population.

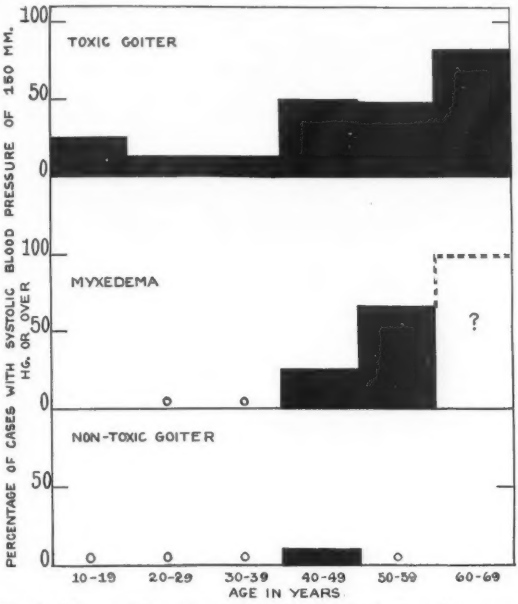

Chart 3. The incidence of hypertension by decades in toxic goiter, myxedema, and non-toxic goiter. The figures for toxic goiter and for myxedema apply only to periods of normal metabolism following treatment.

The great difficulty is that the incidence of hypertension in the general population in unknown [Dublin (2, 2A), Lerman and Means (3)]. The data available are complicated by the fact that readings in different parts of the country are often not taken under the same conditions, posture and slight emotional excitement sometimes causing marked variation. A single determination of the blood pressure is probably of little value in determining the true level. Alvarez (4), on the basis of single determinations, found 22 per cent of male freshmen at the University of California had a systolic blood pressure of 140 or over; while Diehl and Sutherland (5) in the freshmen at Minnesota, and Lee (6) in the freshmen at Harvard found only 3 per cent and about 2 per cent, respectively, of hypertension after repeating

their observations in the cases in which the blood pressure was high at the first reading. The incidence after a single determination was 16 per cent and 12.8 per cent, respectively. Because of the variations that occur, we think it is important to state that our determinations were made with the patients in the recumbent position, that the determinations were repeated frequently in most cases, and that in most instances, at each determination, the reading was repeated until the pressure had become stationary. A mercury sphygmomanometer was used.

Perhaps the best figures for comparison with our data are those of Gager (7), who determined the blood pressure in 1000 women and 1000 men at the Cornell clinic. Because most of our subjects were women we have used only his figures for women in constructing Chart 4. This is fair

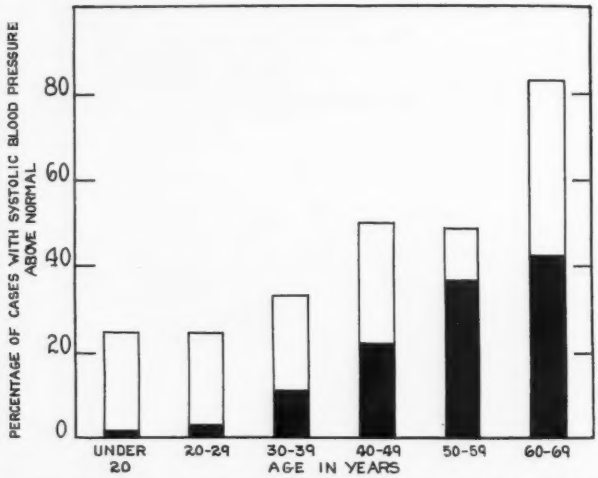

Chart 4. The black areas denote Gager's female patients and the total height of the columns the authors' cases of toxic goiter after treatment. To conform with Gager's data, a systolic blood pressure below 140 mm. mercury is considered normal in persons under the age of 40 and one below 150 after the age of 40.

because the incidence of hypertension was less in his men than in his women. It may be noted that our incidence in both toxic goiter and in myxedema for the various age groups is distinctly higher than his. Moreover, in all his women of 40 years of age and over the systolic blood pressure was 150 or higher in only 30 per cent as compared with 52 per cent and 50 per cent for our cases of toxic goiter and myxedema, respectively. Inasmuch as Dunham (8) in army officers 40 years of age and over found an incidence of hypertension only about half of that in Gager's men of the same age, one wonders whether Gager's figures are not too high. Our figures are not strictly comparable with those of Gager because he eliminated cases of nephritis and we did not. They are roughly comparable, however.

So far as the normal value for the systolic blood pressure is concerned, it may be noted that Symonds (9) of the New York Life Insurance Company found the mortality in patients with a systolic blood pressure of 140 or over greater than the mortality for all insured persons. He, therefore, thinks that a pressure of 140 or over at any age is probably abnormal. Fisher (10) might perhaps place the normal value at a slightly higher level.

In connection with these findings, it is of some interest that arteriosclerosis is common in cases of myxedema that come to autopsy (11). Goetsch's (12) demonstration of a thickening in the intima and media of the superior thyroid arteries in thyrotoxicosis suggests that arterial changes may be common in this condition also. Numerous reports have been made on various types of cardiac damage in thyrotoxicosis, although some observers still claim that the thyroid, per se, causes no changes in the heart but that any changes which occur are the result of the action of an overactive thyroid on a previously damaged heart (13) (14). In any event, the possibility must be considered that a normal thyroid function is of importance in preserving the integrity of the cardiovascular system.

SUMMARY

The incidence of hypertension appears to be greater in patients with toxic goiter and in patients with myxedema after the metabolism has been restored to normal by appropriate treatment, than in the general population.

A diastolic pressure of 100 mm. of mercury or over in both thyrotoxicosis and myxedema before treatment makes it practically certain that a hypertension exists independently.

In patients with toxic goiter, if the systolic pressure is 190 mm. of mercury or over before treatment, it is probable that it will be 150 or over after treatment. In 10 of 53 cases in which a hypertension was present after treatment, the systolic pressure rose to the hypertensive level only after the basal metabolism had been restored to normal.

In about 45 per cent of the cases in which the diastolic pressure ranged from 70 to 99 mm. of mercury before treatment, the systolic pressure was 150 or more after treatment.

In no case in which the systolic pressure was below 130 mm. of mercury before treatment, and in no case in which the diastolic pressure was below 60, was a hypertension present after treatment.

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THE BEARING OF RECENT WORK ON THE ANTERIOR PITUITARY HORMONES UPON GYNECOLOGICAL PROBLEMS, WITH ESPECIAL REFERENCE TO DISORDERS OF MENSTRUATION*

EMIL NOVAK

From the Gynecological Department, Johns Hopkins Medical School

BALTIMORE, MD.

No physiological problem has been more assiduously studied within recent years than has that of the female reproductive cycle. Important advances have been made, and many of these have been directly applicable to the interpretation and management of clinical problems. The debt of gynecology to the research worker in this respect is naturally greater and more clearly apparent than that of any other branch of clinical medicine.

The gynecologist himself is rarely qualified to carry on physiological investigations, although there are not a few important problems which are just as readily, or perhaps even more readily, studied in the human female than in the laboratory animal. In the main, however, the gynecologist has become quite dependent upon the trained laboratory investigators who have interested themselves in this problem, so that nowadays the intelligent practice of gynecology presupposes a familiarity with the interesting story of reproductive physiology which physiologists are unfolding for us. So rapid have been the advances, indeed, that it is as unsafe for the clinician to lose contact with current work as it is for the stock speculator to neglect the daily quotations in times of feverish market activity.

In a recent review (1) I pointed out how some of these physiological advances of the past few years have already made it necessary for us to change our ideas of the mechanism of the menstrual phenomenon. I shall not reconsider these changed viewpoints in this paper, but may summarize them as follows: 1. While ovulation in the human female characteristically precedes menstruation, the belief in its indispensability to the latter no longer seems tenable. 2. The doctrine of the "primacy of the ovum," according to which the germ cell is the regulator of the periodicity of menstruation, must be abandoned. 3. Two ovarian hormones, folliculin and progestin, are concerned in the production of the characteristic cyclical changes in the genital mucosa, so that we may now very properly speak of a follicle phase and a luteal phase. 4. The important role of the anterior pituitary in the activation, and perhaps the regulation, of ovarian cyclical function, has been established.

It is with the last of these conclusions that I shall deal in this paper, because it is this particular problem which has continued to interest physi-

*Read before the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, Pa., June 8, 1931.

ologists more than any other, and which has clinical applications less generally recognized than they should be.

To begin with a problem which is now quite old, that of hypofunction of the anterior hypophyseal lobe, the clinical picture which at once comes to mind is the so-called dystrophia adiposo-genitalis of Fröhlich. While other types of hypopituitarism (Levi-Lorrain type, Neurath-Cushing type) may be seen, the Fröhlich syndrome is the most common and, therefore, the one which has received most attention. Originally described in a case in which there was a definite destructive tumor of the anterior lobe, it has been accepted also as an evidence of mere functional deficiency of the structure. For this belief there has been excellent scientific support in the experimental studies of Pierre Marie, Cushing and his co-workers, and others.

There has, however, been a long drawn out discussion as to whether the anterior lobe is responsible for all the changes characterizing this syndrome, and particularly as to whether the metabolic changes associated with the obesity may not have their source in the portions of the brain immediately contiguous to the gland rather than in the latter itself. The recent studies of Smith (2) would appear to have solved this problem, showing as they do that the metabolic disturbance has its origin, not in the anterior pituitary, but in the adjacent hypothalamic areas of the brain. The rather constant association of obesity with the genital changes of adiposo-genital dystrophy, therefore, is difficult to explain. That a definite hypopituitarism is present is quite generally accepted, and, in spite of Smith's work, it is probable that the syndrome will continue to be spoken of as a hypopituitary one.

It is one which is encountered very frequently in our clinical work, particularly because of the amenorrhea and the sterility which are so often a part of it. Gynecologists would be grateful for the development of a rational method of treatment. At the present time we must content ourselves with the semi-empiric administration of thyroid extract, perhaps some form of ovarian therapy for the amenorrhea, and rather random attempts at a casual therapy by the use of pituitary substances of one form or another, by one route or another. The oral administration of pituitary substance, as practiced by some clinicians, is rather generally derided by laboratory investigators, because of its negative results in animals, and my own observations coincide with this view.

It is possible, though not by any means certain, that the newer work on the separation of the anterior pituitary hormones, to which reference will be made later in this paper, may lead to a more intelligent and successful treatment of this very common syndrome. The recent papers of Cushing and Henderson, for example, offer the first satisfactory explanation for the varying influence of pituitary adenomata upon the sex functions.

A somewhat newer problem has flowed from the classical studies of Smith and Engle (3), and Zondek and Aschheim (4), upon the role played by the anterior lobe in the physiology of the sex cycle. The rather feverish

activity in this field is indicated by the fact that already five hormones are ascribed to the anterior hypophysis, viz.: 1. A follicle-stimulating hormone. 2. A luteinizing hormone. 3. A growth hormone. 4. A metabolic hormone, concerned chiefly with the regulation of the specific dynamic activity. 5. A thyroid-activating hormone. In a recent paper Bugbee, Simond, and Grimes (5) enumerate no less than eleven physiological activities which have been ascribed to the anterior lobe. Much of this early work, of course, will have to be reappraised, probably again and again, as new facts are accumulated.

Especial activity has characterized the study of the pituitary hormones which appear to be so important in the activation of the cyclical function of the ovary. It is worthy of note, too, that almost all of the excellent groups of investigators studying this problem have concluded that there are two separate hormones whose functions are correlated with the two demonstrated hormones of the ovary. It is true that there are some minor differences of opinion as to the details of these interrelationships, but a definite common ground can be seen in the results of Evans and Simpson (6), Zondek (7), and Crew and Wiesner (8) on this point.

The German investigators have pursued the problem perhaps most intensively, and their terminology will be followed in this paper. They give to the combined gonadal principles of the ovary, as found in the urine of early pregnancy, the name Prolan. This, however, is a composite of two hormones secreted by the anterior lobe. One of these, Prolan A, has to do with follicle ripening, and with the motivation of the ovarian follicular hormone. The other, Prolan B, is a luteinizing hormone, concerned with the transformation of granulosal and, under certain conditions, thecal cells, into lutein cells, and, therefore, with the motivation of progestin. In other words, the governing role of the pituitary over the ovary is characterized by a duality consonant with the duality of the pituitary and ovarian hormones. This complicates the picture considerably, as such a mechanism offers possibilities of a much larger number of pathological variations than would a simpler one.

There are other disturbing elements along this line, as will appear from the important recent contributions of Hartman, Firor and Geiling (9). These investigators find that even very large doses of ovarian follicle hormone fail to produce oestrus in monkeys, either normal or castrated, if the animals are previously hypophysectomized. This would appear to indicate that the follicle hormone can produce its effect only through the agency of the hypophysis; in other words, that the follicle hormone is an activator of the anterior lobe, just as the latter activates the former. This, of course, is very confusing.

One other observation of Hartman and his associates is worthy of mention, because of its possible gynecological significance. While large doses of anterior pituitary extracts produce no hypertrophic changes in the genital canal of castrated monkeys, they do, and in comparatively moderate dosage, cause bleeding from the endometrium. Hartman and his co-workers

conclude that the threshold for uterine bleeding is much lower than that for the actual developmental and hypertrophic histological changes of the cycle.

This observation is of great interest when viewed side by side with the studies of Marrian and Parkes (10), who found that in mice about 200 times as much oestrin is necessary to produce copulation, with typical oestrous changes in the uterus, as is required to produce the vaginal cornification changes considered characteristic of oestrus in the ordinary vaginal smear test. On this basis they suggest that in the human patient, weighing approximately 2000 times as much as a mouse, it may properly be assumed that 400,000 mouse units (2,000 x 200) would be necessary to produce corresponding histological changes in the ovaries and uterus by the clinical administration of follicle hormone. This would make the usual efforts at the organotherapy of amenorrhea seem woefully inadequate. Moreover, even if histological changes were brought about, they would not be those seen in the normal menstrual cycle, of which they would represent only the follicular phase. Even if, therefore, bleeding be occasionally noted after such treatment, there should be no self-delusion as to its menstrual character, particularly as the ovaries themselves are untouched by follicle hormone administration.

The observations above noted, especially those of Hartman and his associates, may be of far-reaching importance in the management of some cases of menstrual disorder. To anticipate, they would suggest that the bleeding factor in cases of functional bleeding, whatever it may be, may be much more readily influenced than the more fundamental one concerned with an actual arrest of the histological cycle, as seen in some cases of amenorrhea.

The particular gynecological problem which invites the application of such observations is that of functional uterine bleeding. This is hardly the place for a description of the clinical characteristics of this exceedingly frequent and distressing disorder, and for this I must refer to several previous papers (11). In these, also, I have presented the evidence, which I think quite complete, for considering the condition a genuinely functional one, the immediate disturbance being in the ovaries. The histological findings in these organs are characterized by an absence of corpora lutea or other lutein elements, with the persistence of unruptured Graafian follicles. On the basis of these findings the natural assumption is that the characteristic "hyperplasia of the endometrium" and the associated uterine bleeding are due to an absence of progestin and a relative excess and persistence of the folliculin effect. The histological character of the endometrium in these cases confirms this impression, for it presents what may be looked upon as a hyperoestrus picture.

If this concept be correct, one is justified in the hope that the administration of progestin, if this were available for use in the human, would convert the hyperplastic, non-secretory endometrium into a pregravid one, thus completing the cycle and perhaps causing cessation of the bleeding.

Unfortunately, no preparation of progestin suitable for administration to the human is yet available. On the other hand, we have recently, through the kindness of Parke, Davis and Company, been supplied with a preparation of the luteinizing hormone of the anterior pituitary, and this bids fair to give better and more fundamental results than those which one might expect from progestin.

The preparation is made from the urine of pregnant women, which is rich in Prolan. Both Prolan A and Prolan B are commonly found, but the dominant effect is obviously that of Prolan B, i. e., luteinization. The reason for this, according to Wiesner (12), is that the A principle becomes inert very rapidly, even on standing, and that its maximum effect is reached long before that of the B element. For this reason, the administration of Prolan in large dosage gives a definitely luteinizing effect. For example, Zondek (13) was able, as he says, almost to convert the rabbit ovary into a mass of lutein tissue by from ten to fourteen daily injections of Prolan. The same luteinizing effect has been noted in the research laboratory of Parke, Davis and Company.

Because of the luteinizing properties of the preparation, we felt that we had a rational basis for its use in cases of functional bleeding, particularly in young women, as the alternative of such treatment is in many cases repeated curettage or undesirable radium or x-ray treatment. A preliminary report on this plan of treatment, with a full discussion of its rationale, was made by Hurd and myself at the recent meeting of the American Gynecological Society (14). Our results in 51 cases, many of them of the recurring type, with often a number of previous curettements, were far more satisfactory than those obtained after any other method of organotherapy with which we are familiar. Bleeding was checked in 44 of this series, often with astonishing rapidity.

However, we have been obliged to alter our views as to the manner in which these good results are brought about. Even when bleeding has been profuse and of many weeks duration, it has not infrequently been checked with such remarkable rapidity that the production of luteinization in the ovary could scarcely have played the important role. Such a conversion of granulosa cells into lutein cells would undoubtedly require some time. It would seem much more likely that some other as yet unknown bleeding factor, linked up with the absence of lutein tissue in the ovary, is the one influenced by the preparation we are using. The endometrium in our clinical cases of functional hemorrhage presents the stationary picture of hyperplasia, instead of the successive histological phases of the normal menstrual cycle. Whether the patient is bleeding or not, the endometrial picture is the same. Some other factor, as yet unknown, becomes operative at periodic intervals to produce the periodic bleeding so characteristic of such cases.

It would appear from the investigations of Hartman, Firor and Geiling that the bleeding factor in the endometrium may be much more readily influenced than are those hormonal factors concerned in the production of

the histological changes of the menstrual cycle. At any rate, although our original concept of treatment in these cases appears to be a rational one, and although the results appear to us to bear out our views, the explanation of the mechanism involved must remain open, because of the encounter with the unknown factors above indicated. Perhaps this clinical problem will suggest promising lines of study to those engaged in the experimental investigation of reproductive physiology.

It is scarcely necessary to stress in this paper the great value of one of the practical applications of studies upon the anterior pituitary lobe, namely, the Aschheim-Zondek test for pregnancy, together with the several modifications of it which have been introduced. All are based upon the fact that with the occurrence of pregnancy there is a sudden flare-up in the activity of the anterior pituitary, and that the hormones of the latter pass over in large amounts to the urine.

That the pituitary undergoes hypertrophy during pregnancy has been known for a long time, and it is to this fact that the occasional occurrence of an acromegaloid condition in late pregnancy has been ascribed. This condition is commonly transitory, disappearing after delivery, but in the occasional case may persist as a genuine acromegaly. The latter is especially common after such periods of pituitary hyperactivity as may be presupposed to occur after pregnancy, puberty and the menopause. In acromegaly, however, we have to deal with abnormalities which concern the growth hormone of the hypophysis, rather than those of immediate importance in the gonadal cycle.

Along the same line, I have been much interested in the striking physiological reaction found in the ovaries of patients suffering from hydatidiform mole or chorioepithelioma. The occurrence of an exaggerated lutein reaction under such conditions is manifested often in the form of large multiple lutein cysts. The mechanism involved has been discussed in a recent paper by Koff and myself (15), our conclusion being that the cause of the "hyperreactio luteinalis" in the ovary is an anterior pituitary hyperfunction, due in its turn to the exaggerated trophoblastic stimulus present in these cases of abnormal pregnancy. In one especially striking case we were able to secure confirmation of the participation of the anterior lobe in the process by careful histological study of that structure.

The histology of the pituitary still offers much opportunity for productive study, although the problem is admittedly a rather difficult one. A few fundamental facts, however, appear to be crystallizing out. For example, there seems no longer to be any doubt that the acidophile cells are concerned with the production of the growth hormone, and the basophile cells with the sex hormones of the anterior lobe.

The Aschheim-Zondek test is of great value not only in the diagnosis of early pregnancy, but is also a help in the differential diagnosis of ectopic gestation. Moreover, it has also been shown to be of great value in determining the completeness or incompleteness of removal of trophoblastic tis-

sue in operations for incomplete miscarriage, hydatidiform mole, or chorioepithelioma.

Finally, reference may be made to the use of anterior lobe preparations in the treatment of amenorrhea, when treatment of the latter is indicated. In the vast majority of cases the mere absence of menstruation produces no harmful results, and in many no direct treatment is necessary except reassurance of the patient as to the harmlessness of the condition. I have reviewed this whole subject in a recent paper (16), and I touch upon it here only to indicate that, paradoxical though it may seem, the anterior pituitary luteinizing principle may be rationally employed in cases of amenorrhea, if it be given after priming the endometrium with follicle hormone.

The luteinizing substance, in other words, would take the place of progestin, because of its capacity to produce in the ovary the cells which secrete progestin. The latter as yet can not be procured in a form suitable for administration to the human patient. The sequence of follicle hormone, and Prolan B, for the present, appears to be the nearest approach which we as clinicians can make to a reproduction of the menstrual mechanism as it is believed to occur, and the clinical results, while not brilliant, have appeared to be better than with other available forms of organotherapy. The rationality of this method would seem to be further indicated by the recent work of Fevold, Hisaw and Leonard (17), who show that the follicle ripening and the luteinization hormones of the anterior lobe exhibit the same "one, two" functional relationship as that which characterizes the effect of the follicle hormone and of progestin upon the endometrium.

The above sketchy outline of the applications of the newer physiology of the anterior pituitary to a few of our gynecological problems will at least serve to illustrate the pathetic dependence of the clinician upon the trained investigator for facts which he can apply in his management of clinical problems. So long as we recognize this dependence, and so long as we are willing to follow the line of scientific march rather than cavort ahead of it, we may perhaps be pardoned for an occasional display of over-enthusiasm. After all, the latter is usually due to the fact that we have human beings to cure, just as the laboratory worker has scientific problems to solve.

SUMMARY

In the treatment of amenorrhea, the most logical plan would be the hypodermic injection of folliculin followed by similar administration of progestin. Since the latter is not available for human use, its place may perhaps, for the time being, be taken by anterior pituitary luteinizing hormone. This plan of treatment produces, so far as we know, no permanent stimulating effect upon the ovary.

There is need for a rational treatment of the adiposo-genital dystrophy. For the present we must content ourselves with the empiric or semi-

empiric administration of thyroid extract, perhaps some form of ovarian therapy for the amenorrhea, and rather random efforts at a causal therapy by the use of pituitary preparations.

In functional bleeding Novak and Hurd have obtained excellent results in a large series of cases, many of them young women in whom the only alternative would have been surgery or radiotherapy. The treatment consists of the intramuscular injection of a luteinizing hormone prepared from the urine of pregnant women, by a new technique (to be reported).

Other subjects discussed as illustrating the application of scientific research to clinical problems are the pregnancy tests of Aschheim and Zondek, Friedman and others. These are of value also in determining the completeness or incompleteness of removal of trophoblastic tissue in operations for incomplete miscarriage, hydatidiform mole or chorioepithelioma. Finally, the role of the anterior pituitary in the production of the multiple lutein cysts ("hyperreactio luteinalis") associated with hydatidiform mole and chorioepithelioma is briefly discussed.

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NOTES ON THE RELATION OF IODINE TO GOITRE*

J. F. McCLENDON

From the Laboratory of Physiological Chemistry,
University of Minnesota
MINNEAPOLIS

Since it was clearly shown by Marine that iodide is a prophylactic against goitre in children, there has been a great deal of interest expressed in the subject, but owing to the length of life in man, the observations have necessarily been imperfect. The observations of Marine and Kimball did not show one hundred per cent protection. The accompanying diagram (Fig. 1) shows results of continuation of Marine's work in Switzerland.

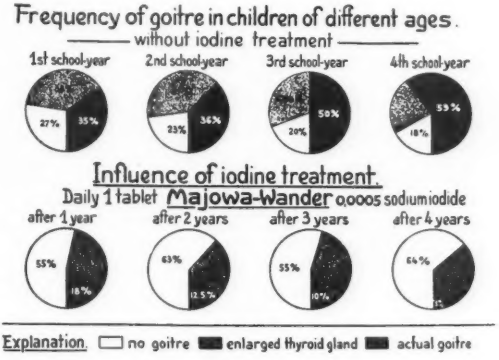

FIG. 1

The most wholesale study has been made in the comparison of Swiss military statistics of goitre in the cantons of Vaud (Waadt) and Freiburg. Each of these cantons has a government salt monopoly. The canton of Vaud owns the salt mines of Bex, and several analyses of the salt of Bex in former times showed the presence of about as much iodine as is now put in the Swiss iodized salt. That did not entirely eliminate goitre in Vaud but enormously reduced it. We might attribute the small amount of goitre remaining to immigration. The canton of Freiburg interdigitates with Vaud and the only difference was the salt, which did not contain appreciable quantities of iodine. The accompanying maps of Stiner (Fig. 2 total goitre, Fig. 3 nodular goitre) show less simple and nodular goitre in Vaud but not as great a difference as reported by Eggenberger.

Some studies which we made on passage of iodine into butter-fat and thyroglobulin indicate that the problem is not entirely settled. Feeding

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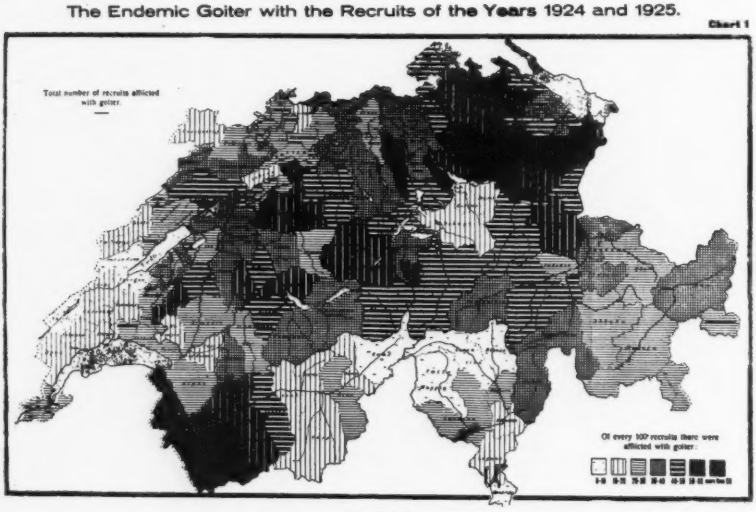
iodine to cows leads to enormous increase of iodine in the watery part of the milk but very little increase in the butter-fat, whereas feeding cows food high in iodine leads to a higher ratio of iodine in the butter-fat to that in the skim milk.

Perhaps a somewhat similar condition is true of thyroglobulin. Thyroglobulin from a normal person contains a high percentage of iodine but


The Endemic Goiter with the Recruits of the Years 1924 and 1925.
Chart 1
Total number of recruits afflicted with goiter.
Of every 100 recruits there were afflicted with goiter:

By Dr. Otto Stoer.

FIG. 2

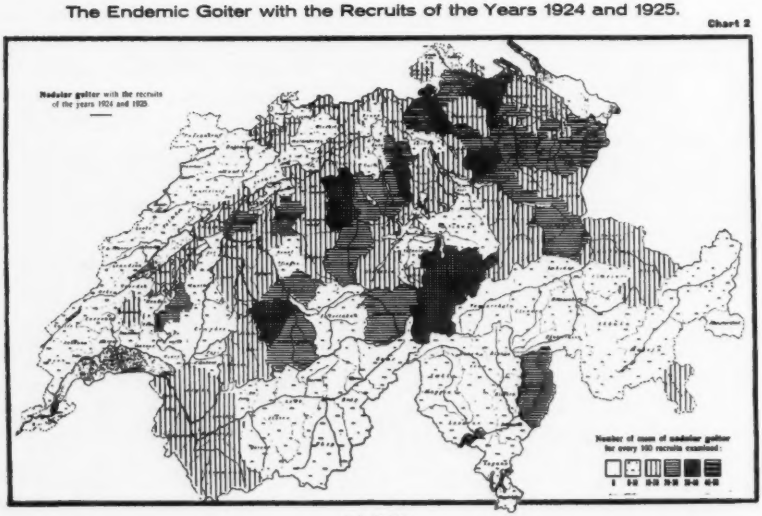

The Endemic Goiter with the Recruits of the Years 1924 and 1925.
Chart 2
Nodular goiter with the recruits of the years 1924 and 1925
Number of cases of nodular goiter for every 100 recruits examined:

FIG. 3

DISTRIBUTION OF IODINE IN COW'S MILK

Town	State	Feed	Iodine in Parts per Billion		* Ratio of Iodine in Butter to That in Skim Milk
			Butterfat	Dry Skim Milk	
Clemson College..	S. C.	Normal.....	78	142	0.9
Byron.....	Ill.	Kelp and seafish.....	176	400	0.7
St. Paul*.....	Minn.	Cod-liver oil.....	36	7,320	0.002
St. Paul.....	Minn.	Iodized oil,** 100 g. daily.....	43	65,600***	0.0006
St. Paul.....	Minn.	Iodized salt containing 10% iodine..	378	158,000	0.0004
St. Paul.....	Minn.	4–5 days after discontinuing iodized salt.....	148	2,800	0.02

*With coöperation of Dairy Division, Department of Agriculture, University of Minnesota.
**Made by adding 20g. of ICl_3 to a gallon of linseed oil.
***Iodine in hulls of fat droplets 26,000.

Drs. Wangensteen, Cavett and I found that the feeding of Lugol's solution to subjects of toxic goitre, which, according to the best studies, contain no appreciable amount of iodine in the thyroid, led to the development of thyroglobulin containing a very small quantity of iodine. It is possible, therefore, that iodine in food, which may be largely diiodotyrosine, may behave differently in the body from inorganic iodine. Prescott in Kendall's laboratory isolated acid-insoluble iodine from hydrolysate of colloid-free cells of exophthalmic goitres that contained no thyroxine. At present we have not sufficient comparative data to decide this question.

Since our laboratory is in a highly goitrous State, and the iodine in local foods was found to be very low, it seemed desirable to have foods from a State much higher in iodine for comparison. In some preliminary analyses the coastal regions of New England were found to be high in iodine but not the western ends. The State of South Carolina appears to be very low in goitre and Remington has made considerable analyses of the iodine content of vegetables. He found spinach to contain about 700 parts of iodine per billion and potatoes averaged 211. His figures for Minnesota potatoes were 86 and the older analyses of mine averaged 71. I have found, however, that there is a loss of iodine in the ashing of potatoes as Remington and I did in our preliminary work. A little better technique by Barrett has given an average of 173 parts of iodine per billion in Minnesota potatoes. It is probable that Barrett's results are comparable to one another, and he found an average of 99 parts of iodine per billion in the potatoes of eastern Minnesota where the goitre is highest and an average of 225 parts per billion in central and western Minnesota where goitre is lowest (Fig. 4 shows goitre per 1000 draft in circles and iodine in potatoes in plain figures.) But the analyses are not to be compared with Remington's older ones; in fact, Remington states that he is finding higher values by improved technique. About all we can say is that the iodine content of South Carolina foods is higher than that of Minnesota. The reason for this appears to be the fact that Minnesota was glaciated and the glaciers removed the soil which probably was high in iodine and dumped a lot of sand and gravel over the State. Remington has shown that sandy soils are much lower in iodine than clay soils of the same

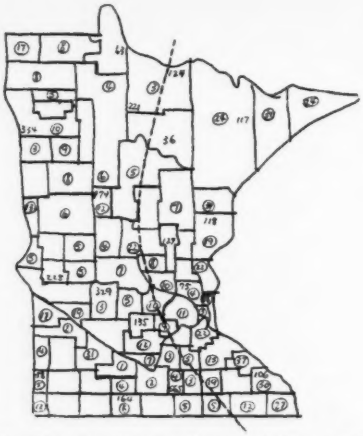


Fig. 4. Minnesota. Number of goiters too large to button a military collar around per 1000 drafted men in the World War in circles. Parts of iodine per billion of dried potatoes in plain figures. The dotted line divides the eastern part (lower in iodine and higher in goiter) from the western part (higher in iodine and lower in goiter).

region. It seems probable that the rain leeches the iodide out of sandy and gravel soils.

Distribution of iodine in relation to goitre has been studied considerably on a large scale by Stiner. After a careful study of Switzerland he concluded that the cooking of the food was the chief factor. The French cooks managed to serve the food with a large proportion of the iodine retained in it, whereas the German cooks threw away the water in which the leafy vegetables were boiled and washed the boiled vegetables in many changes of water, thus removing a great deal of the iodine. He has shown that the German-speaking Swiss have more goitre than the French-speaking Swiss. The cooks did not, however, know anything about iodine and did not purposely add it to foods. It is desirable to start with the food high in iodine as well as to cook it properly.

People do not like to be experimented on over long periods and at the present status of the subject it seemed necessary to experiment on them without their knowing it. I have so far been able to perform only one experiment. In 1911 I started feeding a woman high iodized foods and the result was that her goitre disappeared. Having developed this method, it seemed desirable to try it out on another generation, so in 1914 I selected two families in this goitrous region and fed one family high iodized foods and kept observations on the other as a control. This experiment is continued to the present day. Some of these foods were from South Carolina and others from the New England coast. We did not have analyses on all the foods directly. Some were judged by the analyses of Bourcet. Each family had two children; the children receiving the high iodized foods have normal thyroids. Of the family used as a control, one child died at birth and the other has a goitre. Basal metabolic rates

showed that the children receiving the high iodized foods are normal and the child used as a control has a low basal metabolic rate and despite considerable medical attention has developed a pronounced obesity. From an early age she went to a very wealthy school and a great deal of talk was made about iodized tablets and salt, but the goitre developed nevertheless.

At present our investigations may be summarized as indicating that iodine in any form may act as a prophylactic in goitre, but no exact quantitative relation of iodine to goitre has been worked out. Different forms of iodine have different effects on tadpoles and may have different effects on human subjects. It appears that the most striking fact about goitre is its geographic distribution. The regions low in goitre have iodine in the water and the food. In collaboration with Dr. F. J. Alway I determined the increase in iodine of alfalfa on fertilization with iodine. Without fertilizer there were three parts of iodine per billion of dry alfalfa and with iodine fertilizer there were 970-1545. At present we must depend on foods from non-goitrous regions. We do not know that it is safe to rely on iodized salt and tablets. There is still another consideration. Suppose the world would rid itself of goitre by the use of iodized tablets or salt; most people would then forget about goitre, which might then return with its original severity. If, however, the food-habits are changed so as to eliminate goitre the taste of the food and other characteristics might cause people to continue it, even though they did not know anything of either iodine or goitre. Except for goitre, food deficiency diseases are rare, although we do not know all of the constituents of the diet that are necessary, and most people know very little about nutrition. If we can develop a system of nutrition selected by the nutritional chemist, but not compounded by him, it would be more valuable to the general population than a mixture compounded of purified chemical substances.

A CASE OF DIABETES INSIPIDUS OCCURRING AS A SEQUEL TO EPIDEMIC ENCEPHALITIS

RICHARD W. WHITEHEAD AND WARD DARLEY
Department of Physiology and Pharmacology and Department of Medicine, University of Colorado School of Medicine and Hospitals
DENVER, COLORADO

Although diabetes insipidus is a syndrome rarely seen (14 per 100,000 cases, Fitz [1]), the condition presents many interesting changes from the standpoint of pathological physiology. The condition may appear during recovery from many of the acute infectious diseases and in the last few years diabetes insipidus has been reported with increasing frequency following epidemic encephalitis. Many of the cases occurring as a sequel to this condition present certain symptoms which appear to differ from those seen in other cases of diabetes insipidus. The following case admitted to the medical wards of the Colorado General Hospital is one of this type and we believe a report of it will not be without interest to endocrinologists and internists.

The literature on the general subject of diabetes insipidus has been reviewed recently in a number of admirable papers (2) (3) and (4), and will not be considered at length here.

Case History, Physical Findings, and Progress.

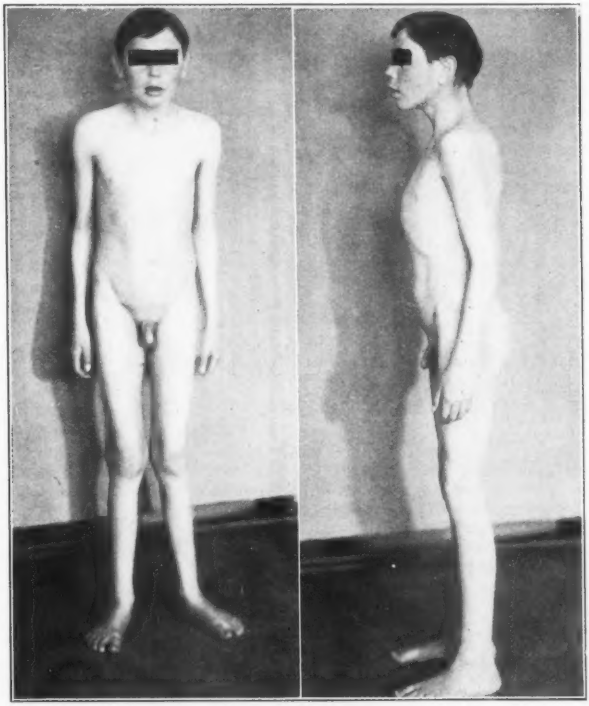
The patient, a boy aged fourteen, was the third of four children. He had been born and reared in Colorado. His birth was normal and at full term. The past history was unimportant except for measles and croup at the age of two and a tonsillectomy at the age of seven. When the boy was nine years of age it was noted that he was becoming nervous, did not sleep well, was drinking and voiding more water than usual, and was always cold. He was forced to quit school, due to urinary frequency. Choreiform movements of both arms and legs gradually developed and he was taken to the Children's Hospital, Denver, where a diagnosis of chronic encephalitis was made. Under treatment the choreiform movements disappeared and the patient returned home. During the next two-year interval the fluid intake and output gradually increased and the insomnia and nervous instability became more pronounced. There was also a gradual increase in his appetite. At eleven years of age the child began to have convulsions, which at first recurred every few weeks and which were always preceded by a prolonged interval of wakefulness. Attacks of vomiting occurred frequently, especially if the patient became excited. Drenching night sweats were not infrequent.

For several weeks prior to hospital entry the convulsions were occurring almost every day and the patient complained bitterly of headache and of inability to sleep. His skin was always moist and he complained constantly of being cold. His appetite was ravenous, he was passing from eight to ten stools a day, and he was drinking and voiding from eight to ten gallons of water every twenty-four hours.

This boy entered the hospital October 30, 1930. He appeared to be most miserable as he lay shivering in bed. Scanning speech as observed in cases of chronic encephalitis was evident. The conjunctivae and sclerae were injected and the eyelids were edematous. Circumoral erythema and chapping were marked and the skin covering the rest of the body was pale, moist and clammy. The thorax was somewhat funnel-shaped, there was some flaring of the ribs, and considerable kyphosis was present. A soft systolic murmur could be heard at the apex. A slight intention tremor involving the upper extremities was noted. The

hands and feet were large and the ankles and feet were moderately edematous. All reflexes were normal. His weight was eighty-three pounds. According to the Stanford Revision of the Binet-Simon Tests he was given an intelligence quotient of sixty-eight.

X-ray studies revealed no abnormality of the sella turcica, lungs, terminal phalanges or long bones. The electrocardiogram showed a slight left axis deviation. The basal metabolic rate was minus 20. The urine had a specific gravity of 1.005, was very pale and the twenty-four-hour specimen contained only 6.1 gm. of sodium chloride. Microscopic examination of the urine was negative. Spinal fluid chemistry and the gold curve were normal. The spinal and blood



Wassermann reactions were negative. The blood hemoglobin was 80 per cent (Dare), the red count 4,500,000 and the white count 2,250, with 66 per cent polymorphonuclears and 34 per cent small lymphocytes. The blood chemistry revealed normal findings as to dextrose, total non-protein nitrogen, urea nitrogen, uric acid, chlorides, calcium, and phosphate. The blood sugar curve following the ingestion of 1.75 gm. glucose per kgm. body weight is graphically represented in Chart 4. This curve will be discussed more in detail later. It should be noted that the one, two, and three-hour specimens collected during the first of these tests were all positive for dextrose (heavy solid line).

The clinical course of this patient can best be followed from the graphic tables represented in Charts 1 and 2. Various laboratory procedures were performed during the first eight days and all treatment was withheld during this period. On the same day that subcutaneous post-pituitary therapy was instituted the patient had a convulsion characterized by generalized tonic, followed by clonic, contractions involving the whole body. After two minutes projectile vomiting terminated the attack. Consciousness was lost during the convulsive period. As long as pituitrin was being administered it is evident that there was an increase in the daily fluid intake and output. It is of probable significance that the other complaints showed no improvement during this period. In view of the apparent inefficiency of pituitrin it was decided to substitute pitressin. Under

this regime (from the 24th to the 27th day) the intake and output rapidly diminished. On the 28th day no pitressin was given and the fluid intake and output more than doubled. After this pitressin was given as indicated until the 69th hospital day. During this second period of pitressin administration the patient's general condition showed steady improvement.

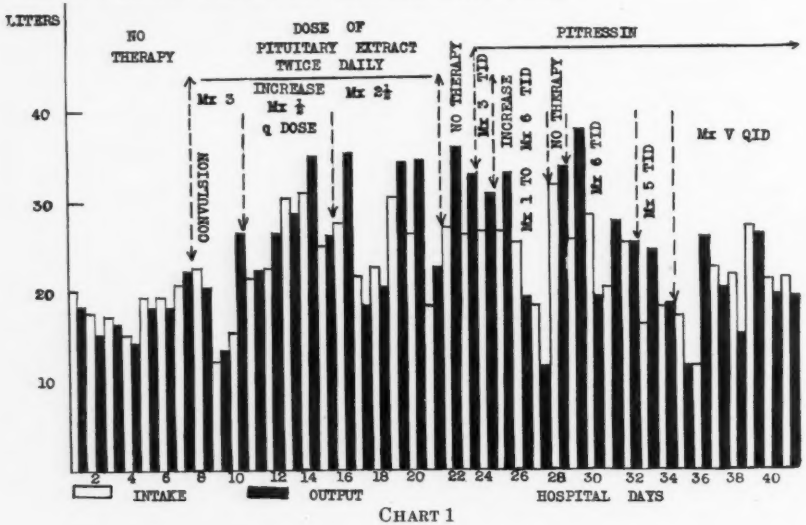


CHART 1

On the 42nd day the patient was given water to drink heated to body temperature and this order was maintained during the remainder of his hospitalization. As a result many of the complaints rapidly improved: he ceased to complain of being cold, the body temperature which had averaged from 96.5° to 97.5° F. approached more nearly the normal level, and his appetite became much more moderate. On the 44th day the boy consumed a quantity of candy. This apparently caused a marked upset in his water balance, from which it took him three days to recover. During the period between the 51st and the 62nd day

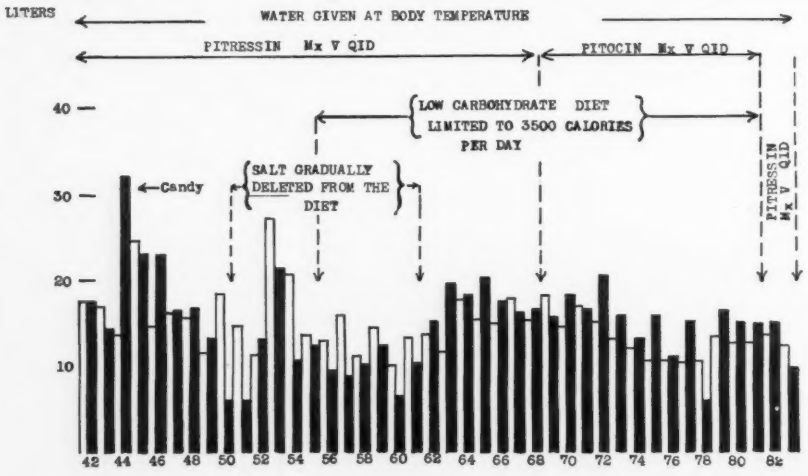

LITERS
WATER GIVEN AT BODY TEMPERATURE
PITRESSIN Mx V QID
PITOCIN Mx V QID
LOW CARBOHYDRATE DIET LIMITED TO 3500 CALORIES PER DAY
SALT GRADUALLY DELETED FROM THE DIET
Candy
PITRESSIN Mx V QID
40
30
20
10
42 44 46 48 50 52 54 56 58 60 62 64 66 68 70 72 74 76 78 80 82

CHART 2

the quantity of table salt consumed by the patient was gradually lessened until none was added to the food. On the 56th day he was placed upon a low carbohydrate diet with the intake limited to 3500 calories per day. These dietary measures were maintained until the patient left the hospital. On the regime as outlined above the boy's mental and emotional condition was greatly improved. He was happy and cheerful during the day and slept satisfactorily at night without sedatives. His water balance seemed better stabilized, although the decrease in the daily intake and output was not as striking as the symptomatic improvement.

Various laboratory tests were again performed after the above observations had been made in order that the results of therapy might better be evaluated. The significant findings and their discussion are given later.

From the 69th day until two days before discharge pitocin administration replaced pitressin. It will be noted that the intake and output varied very slightly, if at all, from that observed during the six preceding days.

The patient was discharged greatly improved January 23, 1931. The routine carried out in the hospital was applied at home and weekly reports indicated that his general condition remained good. He returned to the hospital April 4, 1931, for a week's observation. There was no essential difference in his condition from that found on January 23rd except that he had gained twenty pounds in weight. The basal metabolic rate was minus 15 and, in addition to the routine previously outlined, he was given three grains of desiccated thyroid a day. This elevated the basal rate to minus 11, but with no noticeable change in the fluid intake and output. He was discharged again April 12, 1931.

DISCUSSION

The syndrome of diabetes insipidus has been reported to occur in association with many types of intracranial lesions. Cases following primary and metastatic tumors of the brain, and those secondary to inflammatory conditions of the brain, meninges or hypophysis make up the larger number of cases of diabetes insipidus. In the last few years a considerable number of cases have been reported following epidemic encephalitis (Hall, 5, Hoke, 6, Snell and Rowntree, 7, and Eaves, 8).

The pathological anatomy in the cases which follow epidemic encephalitis has not been studied extensively, but Eaves and Croll (9) have recently reported the finding of definite pathological changes in the hypothalamus. In this region all the nerve cells exhibited chromatolysis and some of them were in the process of destruction and were surrounded by glia cells. Although a sufficient number of these cases have not yet been studied at necropsy to make it possible to draw definite conclusions, Eaves and Croll have made the suggestion from a comparative study of the brains of ten cases of epidemic encephalitis that diabetes insipidus evidently does not occur subsequent to encephalitis when the pathological disturbances in the hypothalamic region are severe; it may occur when they are less severe. This would make it appear likely that the condition is due to an irritative lesion in that part of the brain in contra-distinction to a destructive lesion.

Experimental work reported in recent years tends to show very definitely that diabetes insipidus may occur following a traumatic lesion in the hypothalamic region in which the hypophysis is spared. The early work on this subject by Camus and Roussy (10) and by Aschner (11) has been amply confirmed by later investigators (Houssay and Hug, 12, Bailey and Bremer, 13, and Hanchett, 14). Until recently, however, it has been possible to induce a permanent polyuria in only a part of the animals operated

upon. In 1930, Richter (15) reported the successful production of experimental diabetes insipidus in white rats by operative injury to the hypothalamic region of the brain. The condition is reported to follow the operation in a large proportion of animals. His histological studies have not yet been published so that it is impossible to state the exact location of the lesion which is responsible for the condition. Warner (16) has reported preliminary observations on the location of the lesion in the hypothalamus in a series of dogs showing either transient or permanent polyuria after hypothalamic injury. In one animal which showed a permanent polyuria he found the lesion to be situated in the nucleus tuberis on both sides of the hypothalamus. This lesion extended anteriorly to the level of the anterior hypothalamic nucleus and posteriorly to the level of the infundibular stalk. It appears from these findings that the anterior hypothalamic nucleus and the nucleus tuberis are in some way concerned with the production of experimental polyuria. Further experimental work is required, however, before the question can be definitely settled.

Since injury to the hypothalamic region or disease conditions involving the nuclei in this region can give rise to the syndrome of diabetes insipidus, there has been much written and there has been considerable speculation as to the functional significance of this area of the brain and its possible relationship to the hypophysis. The hypothalamic region and the hypophysis are closely associated both anatomically and developmentally. Histological studies of this region of the brain by Greving (17), Pines (18), Espino (19) and others have revealed that nerve fibres can be traced from the nucleus supraopticus and possibly also the nucleus paraventricularis into the pars neuralis of the hypophysis. Further evidence that the hypophysis may be involved in diabetes insipidus is furnished by the fact that posterior pituitary extracts can be used to control the symptoms of the condition in a large percentage of the cases. While such evidence is somewhat equivocal, it is suggestive and, taken together with other facts, it points strongly to the conclusion that the hypophysis is concerned in the etiology of diabetes insipidus.

Other investigators believe that the hypophysis plays no role in the etiology of diabetes insipidus, but are inclined to attribute the syndrome to alterations in the function of the hypothalamus. Certain investigators have reported finding a diuretic substance in extracts of the hypothalamic region (Olivet, 20, Bourquin, 21). Bourquin has extracted a substance from the region of the brain about the mammilary bodies which induces diuresis in experimental animals. She has also reported finding a substance in the urine of dogs which had previously been rendered polyuric by a traumatic lesion in the hypothalamus. She found this substance would induce polyuria when injected into normal dogs. In our studies on the present case we endeavored to determine whether the urine contained a substance comparable in action to that found by Bourquin in the urine of dogs with a hypothalamic lesion. The substance prepared according to her method was injected intravenously into several rabbits and into a

bladder fistula dog. One experiment on a rabbit and another performed on a dog are given below.

White Rabbit. Weight, 3.7 kgm. Male.
Urine collected from a catheter inserted in bladder.

Time		*Urine Volume*
10:58-11:28		0.5 cc.
11:28-11:58		1.2 cc.
12:22	Intravenous injection of 5 cc. of preparation from urine of case J.B.	
12:22-12:52		2.6 cc.
12:52- 1:22		3.4 cc.
1:22- 1:52		1.8 cc.
1:52- 2:22		0.9 cc.
2:22- 2:52		0.7 cc.
2:52- 3:22		2.3 cc.

The above results indicate that there was considerable diuresis after the injection of the preparation, but a substance similarly prepared from the urine of a normal person gave a comparable increase in urinary output when injected into rabbits.

Bladder Fistula Dog. Weight, 8 kgm. Female.

Time		*Urine Volume*
1:45-1:55		2.2 cc.
1:55-2:05		1.8 cc.
2:10	Intravenous injection of 5 cc. of preparation from urine of case J.B.	
2:10-2:20		2.3 cc.
2:20-2:30		1.8 cc.
2:30-2:40		1.2 cc.
2:40-2:50		1.6 cc.
2:50-3:00		1.0 cc.
3:00-3:10		1.4 cc.

The above experiment on the dog and others similarly performed gave negative results. These experiments failed to confirm Bourquin's observations on a human case of diabetes insipidus. The results here, however, are complicated by the fact that we were injecting a considerable amount of foreign protein into the animals and this might have been concerned in the production of the negative findings.

The classical symptoms of the syndrome of diabetes insipidus were present in this case and there was little doubt as to the diagnosis. The high fluid intake and the marked polyuria which this patient showed before entrance into the hospital marks the case as one of more than average severity. Many of the other symptoms which the patient presented on admission to the hospital have been observed in other cases of diabetes insipidus and have been attributed to the alterations brought about in the body economy by the excess fluid intake. Other symptoms in this case, such as scanning speech and the intention tremor, were undoubtedly residual to the encephalitis. Accompanying the large fluid intake the patient had headache, vomiting, diarrhea, sweating, edema, insomnia, and convulsions. This entire group of symptoms could have been due to water intoxication. Similar

symptoms were reported by Rowntree (22) to occur in dogs, to which large quantities of water were given and other cases reported by Snell and Rowntree (7) indicate that these symptoms may be expected to follow the ingestion of large amounts of water in man. The mental state of the patient was in all probability due in part to water intoxication since there was such marked improvement when pitressin was given.

Several of the symptoms observed can no doubt be attributed to the functional alterations brought about by the excessive ingestion of cold water. The polyphagia has been explained (Snell and Rowntree, 7), as due to an attempt on the part of the body to overcome the heat debt created by the ingestion of such a large volume of cold water. The vasomotor disturbances, chilliness and shivering may be attributed to the same cause.

As previously noted, the results of the various therapeutic procedures instituted upon the urinary volume and water intake are shown in Charts 1 and 2. After several days' hospital stay, during which numerous laboratory tests were made, the patient was placed on post-pituitary extract therapy. The results of administration of pituitary extract (posterior lobe) were in many respects directly opposite to those obtained in certain other cases of diabetes insipidus and, instead of improving, his general condition was made worse by it. Our observations on the action of posterior pituitary extract in this case correspond to those of Snell and Rowntree (7) who reported that cases of diabetes insipidus which follow epidemic encephalitis are refractory to pituitary extract.

In 1928, Kamm, Aldrich and co-workers (23) discovered that the posterior lobe of the hypophysis contained two active principles, one of which stimulates the cardiovascular system and raises the blood pressure; the other appears to be quite lacking in pressor activity but stimulates uterine muscle to contract. The former substance is called "Pitressin," the latter "Pitocin."

Soon after their separation these substances were tested on experimental animals to determine their effect on the urinary output. Bugbee and Simond (24), using rabbits, determined that pitressin is much more antidiuretic than pitocin. Hemingway and Peterson (25) investigated the antidiuretic action of pitocin and pitressin upon the heart-lung-kidney preparation and upon water diuresis in man. Added to the blood in the isolated kidney preparation both pitressin and pitocin reduced the output of urine and increased the concentration of the urinary chlorides. Diuresis in man was inhibited by both extracts, but pitressin was found to be twenty times more powerful than pitocin. They suggest that the antidiuretic action of pitocin may be due to imperfect separation from the pressor principle. Burn (26) found that pitocin was practically lacking in antidiuretic activity, while pitressin had marked antidiuretic power. The latter was found to be the same per unit of pressor activity as in a sample of pituitrin. Burns' results suggest that pitressin is the antidiuretic principle of posterior lobe extracts. Draper's (27) results suggest another explanation for the antidiuresis produced by posterior lobe extracts. He has obtained evi-

dence, using bladder fistula dogs as test animals, that there may be a third hormone in posterior lobe pituitary extracts which, depending upon the condition of the water balance in the animal, may be responsible for diuresis or antidiuresis.

Clinically pitressin has been used successfully in the treatment of diabetes insipidus by several investigators (28, 29, 30). In the present case its administration was followed by a definite reduction in the water exchange and finally a stabilization at a lower level. (See Charts 1 and 2.) Chart 3

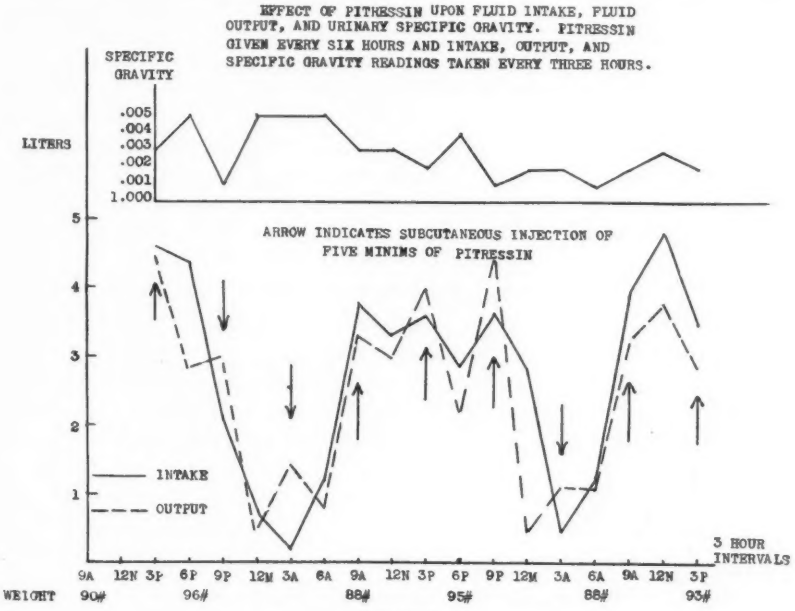

EFFECT OF PITRESSIN UPON FLUID INTAKE, FLUID OUTPUT, AND URINARY SPECIFIC GRAVITY. PITRESSIN GIVEN EVERY SIX HOURS AND INTAKE, OUTPUT, AND SPECIFIC GRAVITY READINGS TAKEN EVERY THREE HOURS.
SPECIFIC GRAVITY
.005
.004
.003
.002
.001
1.000
LITERS
5
4
3
2
1
ARROW INDICATES SUBCUTANEOUS INJECTION OF FIVE MINIMS OF PITRESSIN
INTAKE
OUTPUT
3 HOUR INTERVALS
9A 12N 3P 6P 9P 12M 3A 6A 9A 12N 3P 6P 9P 12M 3A 6A 9A 12N 3P
WEIGHT 90# 96# 88# 95# 88# 93#

CHART 3

gives further information on the action of pitressin upon the urinary output and urine specific gravity. The chart represents the effect on the water intake and excretion and urine specific gravity when pitressin was administered every six hours. (Water intake, urinary output, and specific gravity readings were recorded every three hours.) In general, it will be noted that both output and intake dropped during the night. The urine volume tended to decrease and the specific gravity to increase during the three-hour period following pitressin administration. The volume output tended to increase and the specific gravity to decrease during the three-hour period preceding pitressin administration. These results show clearly that pitressin had only a temporary antidiuretic effect, which tended to disappear in three hours or less. Similar observations by Snell and Rowntree (7) indicate that pituitary extract (posterior lobe) likewise has only a temporary antidiuretic effect in some cases of diabetes insipidus. The patient was weighed twice a day, and it was found that the lowest weights were found

in the mornings, after a period when the output had exceeded the intake and that they were highest in the late afternoon, when the intake had exceeded the output.

In the attempt to obtain direct information relative to the etiology of the polyphagia, chilliness and vasomotor disturbances, we decided to give the patient water to drink, which was warmed to body temperature. Following this it was noted that he complained less of being chilly, and that his appetite became less ravenous. These results indicate clearly that the polyphagia was probably a compensatory phenomenon, which tended to overcome the heat debt created by the drinking of large amounts of cold water.

Further studies in the case were made to determine if possible whether the salt and carbohydrate intake was associated in some manner with the polyuria. The salt intake was only gradually reduced, beginning with the 51st hospital day. By the 62nd day no salt was added to the diet. There seems to have been no marked alteration in the water exchange which could be correlated with the reduction of salt intake.

It had been noted in the period before pitressin administration was started that the patient's glucose tolerance was abnormal (Chart 4, heavy

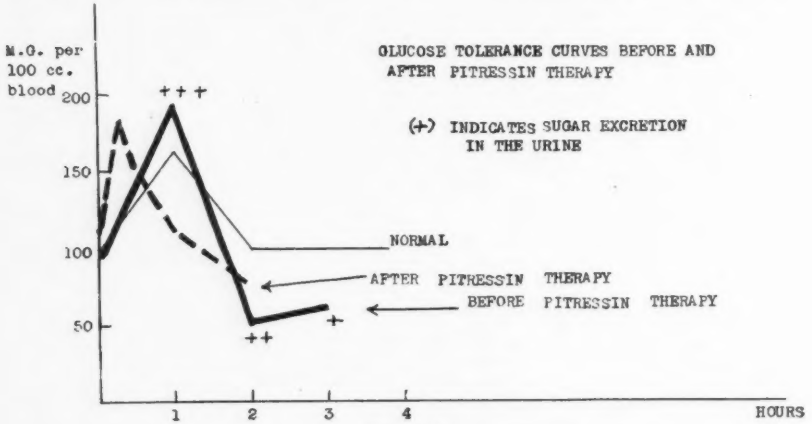


CHART 4

solid line). It will be noted that the blood sugar exceeded the normal the first hour following the administration of glucose. At the second and third hour the blood sugar was far below the control reading, and even below the normal. Glucose was found in the urine on the first, second and third hour. The results of a second glucose tolerance test taken after the exhibition of pitressin for several weeks is also shown (interrupted line). Here it will be seen that the tolerance curve approaches closer to the normal, but that the reading taken the second hour was again far below the control level. Glycosuria did not occur during this test. It is probable, therefore, that the patient originally had a low renal threshold for glucose and that pitressin

raised it somewhat but not to the normal level. From these observations and from the fact observed, clinically, that the patient consumed a larger amount of water and excreted more urine for three days following the taking of candy (Chart 2, the 44th through the 46th day), is was decided to eliminate added sweets from the diet and to reduce the carbohydrate intake with a corresponding reduction in the daily caloric intake from about 4,000 to 3,500 calories. This was done on the 56th day and appeared to stabilize the water balance somewhat.

On the 62nd day a twenty-four-hour specimen of urine was collected and examined as had been done before therapy was instituted. Briefly, the comparison is as follows:

	Before Therapy	*After Therapy*
Volume	22,050 cc.	4,380 cc.
Specific gravity	1.006	1.008
Grams Sodium Chloride	6.1	17.72

In comparing the twenty-four-hour specimens taken before and after therapy it will be noted that the volume had diminished to approximately one-fifth, that the specific gravity was slightly higher, and that the sodium chloride content was increased approximately three times. These results would naturally be expected with a more highly concentrated urine.

Although pitocin has relatively slight antidiuretic action in normal subjects it was deemed best to study its effect upon this patient. Consequently, upon the 69th day, pitocin replaced pitressin administration. Following this the boy's condition showed no significant change. This might indicate that warm water administration and dietary restriction played some part in maintaining the low water exchange previously established by pitressin.

SUMMARY AND CONCLUSION

A case of diabetes insipidus of more than average severity is presented which evidently had its origin as a sequel to epidemic encephalitis. On admission to the hospital the case showed marked polyuria, polydipsia, and many symptoms of water intoxication.

Treatment with posterior lobe pituitary extract failed to reduce the diuresis or water intake, and even aggravated the condition. Pitressin therapy was more effective in reducing the fluid intake and excretion, and it was found possible to maintain the water exchange on a much lower level than when the patient entered the hospital. The signs of water intoxication gradually disappeared under pitressin therapy. Other therapeutic measures included giving the patient warm water to drink and reducing the carbohydrate and salt intake. Reduction of the carbohydrate intake apparently aided in stabilizing the fluid exchange.

Pitocin was substituted for pitressin for a period of eleven days. During this time there was no marked change in the urine volume or fluid intake over a similar period when pitressin was given. It is difficult to

evaluate these findings, but at least it can be said that pitocin did not aggravate the condition.

A continuation of the treatment as outlined has apparently resulted in a sustained symptomatic improvement.

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FAMILIAL HYPOTHYROIDISM*

A Clinical Study.

E. KOST SHELTON, M.D.
SANTA BARBARA, CALIF.

This study of familial hypothyroidism is presented (1) to discuss the frequently unrecognized occurrence in America, (2) to demonstrate the practical value of osseous development as an aid to diagnosis, (3) to enlist the interest of clinicians in the allergic manifestation observed therein, and (4) to show the effect of treatment.

Endemic cretinism, so common in sections of Europe, is rarely seen, or at least seldom recognized, in America. The fact is due, not alone to its relative scarcity in this country, but to its relative benignity as well. Such a severe expression of hypothyroidism as the classic textbook picture of cretinism has a tendency to cloud the finer diagnostic sensibilities of physicians. It is obvious that one need not be a gnome-like imbecile with a thick protruding tongue, a pot belly, and coarse dry bristles, to be classed as hypothyroid; and yet, at times, this gross misconception seems to obtain. In addition to the so-called cretinic degeneration, such limiting terms as endemic goiter and infantile myxedema tend to confuse. Conceding a variable symptomatology in these conditions, they appear, at least, to have one thing in common, i. e., hypothyroidism. If the variability cannot be explained on a basis of degree or the length of time to which the patient has been subjected, no one has, as yet, devised a more adequate explanation.

One is impressed with the splendid work of Kimball and Marinus (1), among the retarded children in Michigan. We have waited long to recognize the insidious menace of congenital hypothyroidism in the goiter belts of America. One should not forget, however, that with a shifting population the condition is not limited to any particular section; neither, as these observers have shown, is visible or palpable goiter an essential feature of the hypothyroid state. While it is true that the thyroid hormones are essential to the normal body economy, and their withdrawal frequently occasions a complex symptomatology, it is equally true that the very simplicity of some hypothyroid conditions defeats the diagnosis. One sees hypothyroidism with and without goiter; with and without myxedema; with and without other stigmata that go to make up a classic picture of thyroid insufficiency.

If we are to believe that the thyroid hormones play a significant role in development, more particularly of the bony framework and central nervous system, it is imperative that the diagnosis of congenital hypothy-

*Read before the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, Pa., June 8, 1931.

roidism be made as early as possible. Space does not permit a discussion of the preventive possibilities during prenatal life. Development continues for many years after birth. It is with this period I wish to deal. The reflection of a mild degree of hypothyroidism on the soma is as insidious as development itself. To wait, before making a diagnosis, until all the classic features of a long standing deficiency are reflected in the physical and mental make-up, is to lose irreparably the most plastic period of the child's existence.

Of late years, calorimetry has made the diagnosis of hypothyroidism comparatively simple in the adult. The same method, however, is of doubtful value below the age of eight. If we are not to depend too largely upon hasty clinical judgment, other diagnostic methods must be employed.

As far back as 1896, Hertoghe pointed out a retardation of carpal development in juvenile hypothyroidism. Engelbach and McMahon (2), much later, enlarged the study to include other joints, and advocated its use as a diagnostic method in the endocrinopathies. Recently, I (3) have attempted to correlate these findings and bring the subject up to date. While it is true that no one can say with certainty just what constitutes a definite normal for a given age, the observation of many children, who were considered free from all stigmata of metabolic disorder, revealed a remarkable conformity of carpal development. Given a reasonable variation from this standard of comparison, the method becomes no more empirical than a basal metabolic rate, a blood count, or other laboratory methods, the interpretation of which must ever be tempered by clinical judgment.

The family I wish to discuss belongs to this large group of mild hypothyroid sufferers so commonly overlooked. No one of the six has ever had visible goiter, and certainly no one presents the classic picture of either myxedema or the cretinic degeneration.

The father, aged 51 yrs., height 68.2 ins., weight 146.6 lbs., is a physician of high standing and more than average intelligence. He was born and reared in California and enjoys excellent health. His basal rate, while always on the minus side, has been found to be consistently within normal limits. He has never had goiter himself and is not aware of any goiter or other endocrinopathy in his family.

The mother, aged 43 yrs., height 60.9 ins., weight 177.5 lbs., is a graduate nurse. She also was born and reared in California, but her father was a native of Someo, Ticino Canton, Switzerland, a village only a few miles from Belanzona, notorious for its goitrous cretins. She has never been aware of any goitrous tendency in herself or family. She is a very intelligent woman and, aside from moderate obesity and slowness of speech, presents no definite evidence of hypothyroidism. The only pertinent factors in her history are a very early onset of catamenia (9 yrs.) and an aggravated form of hay fever and mild paroxysmal asthma, from which she suffered between the ages of 16 and 40 years. During this period she bore

four children, underwent several nose operations, took quantities of medicine and had innumerable tests. At 40, without the benefit of a basal metabolic rate determination, she was advised to try thyroid. She started taking one grain daily and has never had an attack of hay fever or asthma since beginning treatment (approximately four years). When she goes without medication for a few weeks, allergic symptoms, manifested by hypersensitiveness of the rhinal mucous membrane, reappear. She is always able to prevent an attack with a few grains of thyroid. In order to complete this record, the patient was urged to have a basal metabolic rate, which in a distant city, was found to be —42 per cent. Later, in our clinic, it was estimated at —37 per cent. She is maintaining well being on 3 grains of thyroid daily—has lost some weight and is feeling entirely normal.

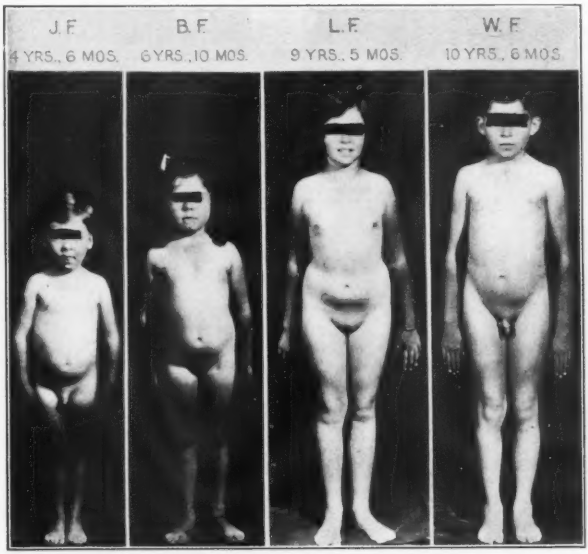

Fig. 1. Photographs of four siblings showing familial hypothyroidism.

Upon the advice of an orthodontist, Mrs. F. consulted Dr. Wm. Engelbach regarding her children, who in turn referred them to me for investigation.

The children are: boys, J. F., aged 4 yrs. 6 mos., and W. F., 10 yrs. 6 mos.; girls, B. F., 6 yrs. 10 mos., and L. F., 9 yrs. 5 mos. They have all had the usual childhood infections, undergone the usual tonsil and adenoid operations, and were reared according to the most approved methods of the day. The two older children suffered severe anaphylactic reactions some years ago when they were given a first dose of toxin-antitoxin. This was not repeated and they, together with the younger children, have since

been guarded from all sources of sera. None of the four has ever presented evidence of rickets, asthma, hay fever, or eczema. The older children are very irritable at times, otherwise their behavior is probably normal. The younger children are of a happy disposition.

B. F., L. F. and W. F. are in the 1st, 4th and 5th grades respectively. The youngest child has not entered school. The child, B. F., in the first grade, seems interested and intelligent. The oldest girl, L. F., gets along exceptionally well, but the parents have noticed that the oldest boy, W. F., has been getting very poor grades, especially in the last two years, and feel that his mental reactions are sluggish, if not definitely retarded.

The only complaint advanced by the mother at the time of examination was one of arrested development. She had found practically no gain in height in any of her children during the previous year and six months.

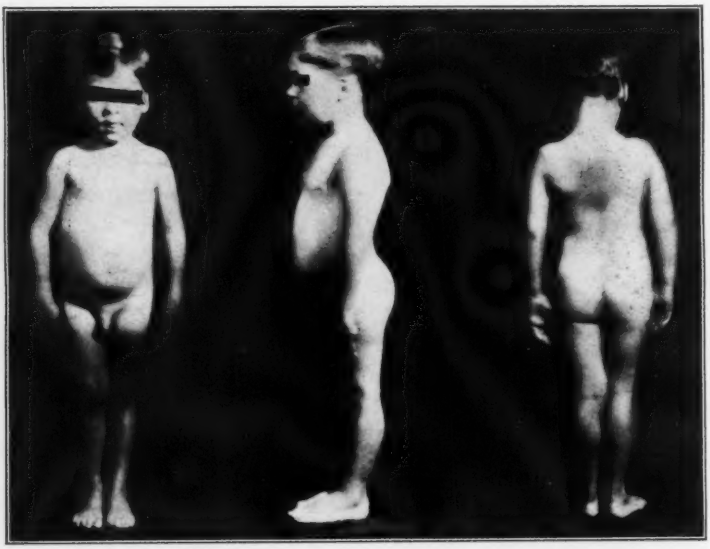

Fig. 2. J. F., Age 4 years, 6 months. Osseous development equals 2 years, 6 months.

On examination, all of the children were found to be under stature according to the accepted standards for their age. Two of them were several pounds underweight and two were several pounds overweight for their height. All, with the exception of the girl, L. F., aged 9 yrs. 5 mos., had exaggerated lordosis, retroussé noses, and very prominent abdomens. All had malocclusion, necessitating orthodontial correction. The two boys and youngest girl had a marked hirsutism, particularly of the back and in in the sacral fossa. The urine composition, the blood chemistry, the blood picture, and the Kahn and Kolmer serological reactions, were essentially normal in all. Sella and thymus pictures did not reveal any departure from the normal.

Considering them separately, W. F., the oldest boy, does not show the intelligence and acumen for one of his age. He has a bilateral cryptorchism, but with considerable effort both testicles may be pushed down into the scrotal sac. The genital development is definitely retarded. He was found to have a —20 per cent and —25 per cent basal metabolic rate.

The oldest girl, L. F., was much more alert than her brother, had a normal posture, and was by far the best developed of the four. She was found to have a —21.7 per cent and —26 per cent basal metabolic rate.

B. F. is considerably overweight. She has a full, rounded, pudgy-looking face and a poor posture.

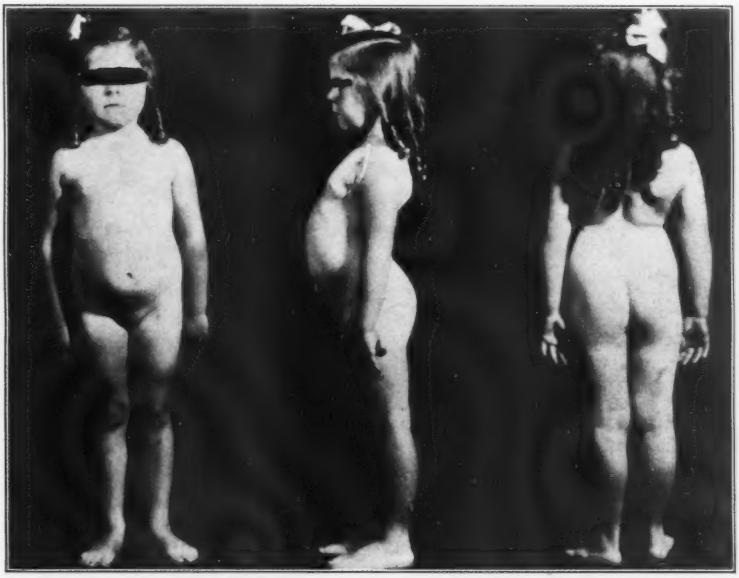

Fig. 3. B. F., Age 6 years, 10 months. Osseous development equals 5 years.

J. F. is not nearly so cretinoid as one might infer from his picture, although he presents many features which should make one suspect hypothyroidism. Basal metabolic estimations were not attempted in the younger children.

The most instructive part of the examination came through a correlation of the osseous development with the findings already related.

J. F., 4 yrs. 6 mos., was found to have the carpal development equal to the normal for not over 2½ yrs. of age, an approximate two year retardation; B. F., 6 yrs. 10 mos., was found to have the carpal development equal to the normal for not over 5 yrs., also an approximate two year retardation; L. F., 9 yrs. 5 mos., had no apparent retardation of carpal

development, which is interesting in view of the low basal rate. It is assumed that this child has not suffered from any severe degree of hypothyroidism until quite recently, a contention borne out by the absence of practically all external stigmata common to the other children. Possibly she is on the way to an early onset of the catamenia and other factors, *i. e.*, the pituitary and gonads have influenced her development in the proper direction. Also one must consider that ossification is naturally more rapid in the female than in the male. Sex, however, does not account for this finding alone, as evidenced by the osseous retardation in her younger sister, B. F., aged 6 yrs. 10 mos.

W. F., 10 yrs. 6 mos., was found to have the carpal development equal to a normal for not over 5 yrs. 6 mos., a retardation of approximately

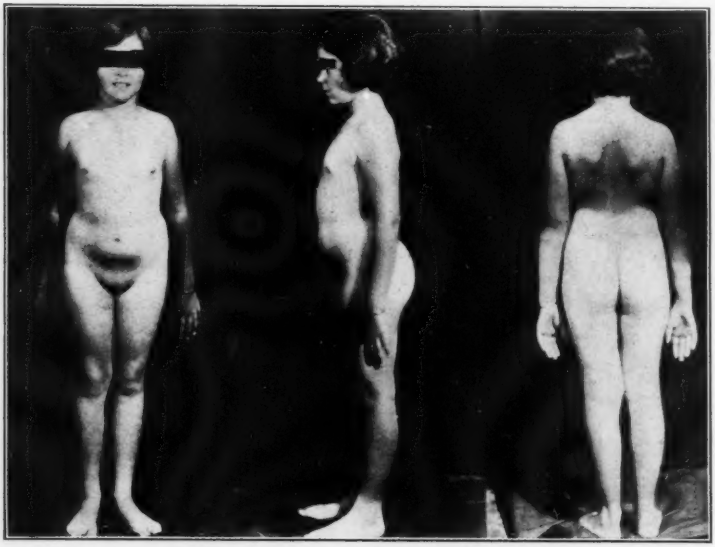

Fig. 4. L. F., Age 9 years, 5 months. Osseous development equals 9 years. B. M. R. —21.7%, —26.0%.

five years. The remarkable difference becomes more apparent when one compares his wrist with that of his younger sister and with that of the six year normal. The head of the ulna is still absent and there are only six poorly developed centers instead of seven, or (if one counts the pisiform, which is usually present at ten) eight well developed centers.

From a roentgenographic study of 1300 children conducted by Baldwin, Busby, and Garside (4), at the University of Iowa, it was found that there was a remarkable variation in the time of ossification of the carpal centers. To me, this is very inconclusive and comparable to a study of a like number of children, possibly the same children, wherein one would undoubtedly find the intelligence quotient ranging from 75 to 175, or the

temperature from 97 to 102. Surely, just as we have a fairly average normal standard in both of these things, so we must have in bony development. Is it not possible that many of these children, considered normal according to the older conception of disease, are actually suffering from a severe degree of metabolic imbalance? I am convinced, had this family been used in a similar investigation, they would have been considered normal. At least, many pediatricians, including their father, have thought of them as such.

The four children were placed on increasing doses of desiccated thyroid by mouth without other medication. It was felt, that, while at least two of them presented evidence of a concomitant pituitary deficiency, monoglandular therapy afforded a much better opportunity for well-controlled clinical observation.

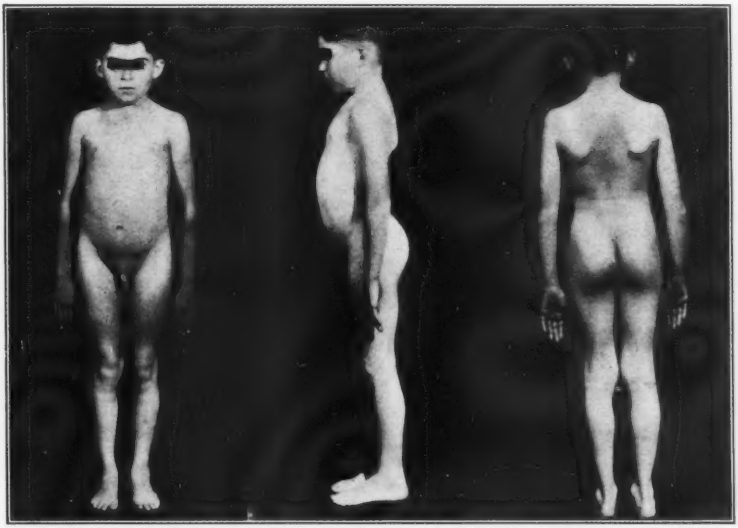

Fig. 5. W. F., Age 10 years, 6 months. Osseous development equals 5 years. B. M. R. —20.0%, —25.0%.

A check up exactly six months after the original examination revealed the following.

J. F. had made a gain of 1 inch in height and 1 pound in weight. His gain was less than any of the others, due perhaps to an acute illness in the spring and the fact that only small doses of thyroid were given him in the early months of treatment. In spite of this, there was a very definite improvement in his somatic makeup.

B. F. had gained 1.4 inches in height and 2.3 pounds in weight. She still retained the chubby rounded contour observed at the first examination.

L. F. had gained 1.3 inches in height and 0.2 pound in weight. In spite of no apparent weight gain, she had developed a rather noticeable

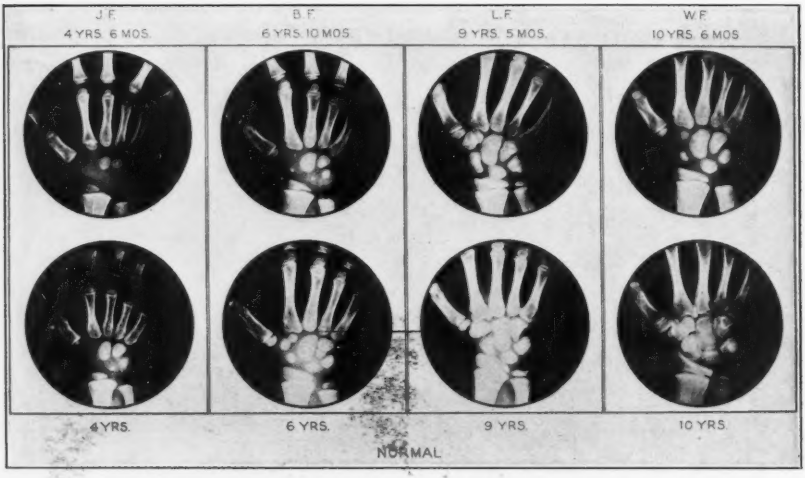

Fig. 6. Skiagrams of the wrists of the four subjects (upper row) and of four normal subjects of similar ages (lower row).

deposit of fat over the upper abdomen. She continued to do well in school and was showing a few signs of the onset of adolescence. Her last basal rate was within normal limits.

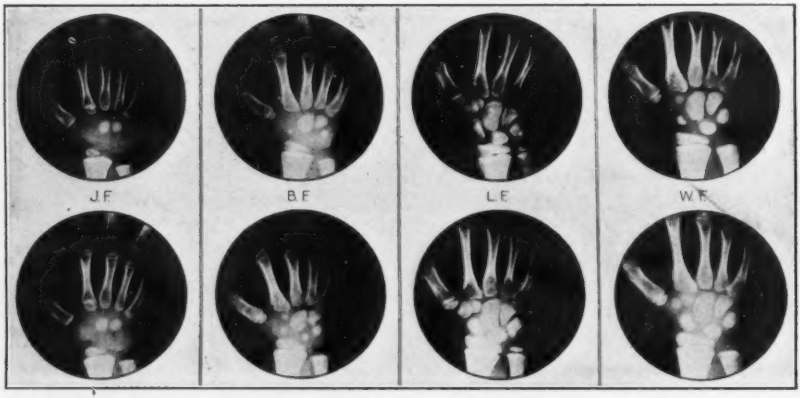

Fig. 7. Skiagrams of the wrists of four subjects (upper row) and the same subjects six months after treatment (lower row).

W. F. had made a gain in height of 1.9 inches and a gain in weight of 1.7 pounds. Both testicles remained permanently in the scrotal sack and his genital development had almost doubled. His teachers reported very

much better progress in school and say that he is much more alert and less irritable. His last basal rate was —9 per cent.

Considering that the mother of these children had noticed practically no height gain in any of them (by the kitchen door method) for nearly two years, and that they are now making (in three cases exceeding) the average normal growth increment, the stimulating effect of treatment becomes more apparent.

Last, the roentgen examinations made exactly six months after the original, corroborate the developmental stimulation in a graphic manner. I must again plead inadequate thyroid plus recent illness for the poor showing of J. F. W. F. presents a rounding out of the lunate, trapezium, and scaphoid which appeared only as tiny dots in the original. The distal epiphysis of the ulna normally present at six has begun to ossify. L. F., who had an approximate normal carpal development at the beginning, shows a better massing of the wrist bones. Again, W. F., who was the most

TABLE SHOWING INCREMENTS IN HEIGHT OF FOUR SUBJECTS OVER PERIOD OF SIX MONTHS UNDER TREATMENT AND COMPARISON OF INCREMENTS WITH NORMAL

Patient	Height			Increment of Patient on Basis of Year	Average Normal Yearly Increment for Age
	Nov. 15, 1930	May 15, 1931	Gain in 6 Months		
J. F.	38.7	39.7	1.0	2.0	2.5
B. F.	42.6	44.0	1.4	2.8	2.2
L. F.	49.8	51.1	1.3	2.6	2.1
W. F.	50.9	52.8	1.9	3.8	2.0

retarded, appears to have made the greatest gain. You will notice that the trapezoid which was entirely absent has not only ossified, but is quite large. The trapezium and scaphoid, which were small and distorted, have rounded out and have become quite large, and the distal epiphysis of the ulna, of which no trace could be found in the original, has ossified and filled out to a considerable degree.

Of course no one can say with certainty what may have occurred in the case of B. F. and W. F. without thyroid substitution, but considering the fact that both had fallen far behind in carpal development and that the latter now shows a gain in six months commensurate to a period of over a year, the effect of treatment seems apparent.

It is hoped this family may be observed for an extended period.

34 West Micheltorena Street

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STUDIES ON PITUITARY FUNCTIONS*

OSCAR RIDDLE
Carnegie Institution of Washington, Station for Experimental Evolution
COLD SPRING HARBOR, N. Y.

Since 1921 our laboratory has been making an attempt, with a fairly common laboratory animal, to separate any existing and separable hereditary levels of pituitary function into different races or strains. If this attempt proves successful we should be able to examine, to very great advantage, the role of the various pituitary functions in the adult life *and in the whole of the ontogenetic development of the individual.* It is still too early to venture a report upon this, our main, pituitary problem; but, in this prolonged and difficult task we are trying to utilize the disclosures made in this field by others, and—somewhat incidentally—we have been led to a few observations of our own. Four of these points can be discussed here.

THE IMMATURE DOVE OR PIGEON TESTIS AS A TEST OBJECT FOR THE MATURITY HORMONE

The testis of the immature dove or pigeon now seems to provide the most sensitive known test for the maturity principle of the pituitary when this is administered in the form of an extract. It was earlier shown (Riddle

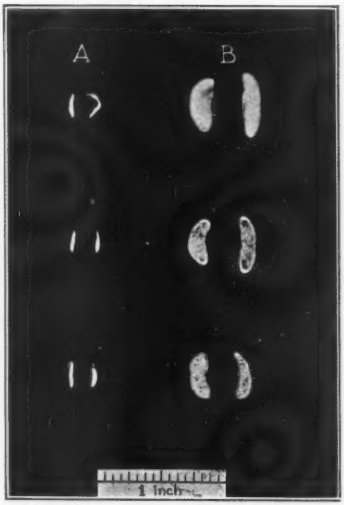

Fig. 1. Three pairs of testes under *A*, control. Ring doves, about 75 days after hatching. Under *B*, testes of brothers of same age (to corresponding figure at left), injected 10 days with anterior pituitary extract.

*Read before the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, June 8, 1931.

and Flemion, 1928) that these testes respond to various forms of anterior lobe administration, though relatively lightly to tissue transplantation; also, that the ovary of birds is less sensitive than the testis to the maturity hormone. It is now found that daily injections of a potent extract may bring about 1500-2000 per cent of extra growth (weight) in the ring dove testis in 10 days (Fig. 1). This phenomenal increase in weight is characterized by a true growth and differentiation of testis tubules already present (Figs. 2

Fig. 2. Cross section of center of right testis of a dove (No. F114); 10 blank injections; control of testis of Fig. 3.

and 3). Dosage over a shorter period is relatively less effective; three to five daily injections may be expected to show an extra increase in testis weight of about 50 per cent per day over their untreated controls. Riddle

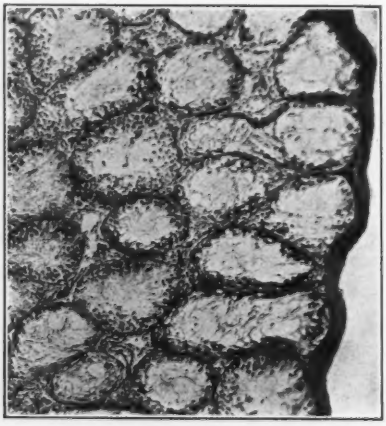

Fig. 3. Fragments of cross section of right testis of brother to control (F114), after 10 daily injections of anterior pituitary extract. Same magnification as Fig. 2.

and Polhemus (1931) have now shown that the response of the testis to the injected maturity principle is at least three to five times greater than that of the ovary; also that these immature testes of dove or pigeon, after only three or four daily injections, clearly demonstrate the presence of the maturity principle in the commercial product, antuitrin. Identical tests made on immature ovaries fail to show the presence of this principle in antuitrin.

The character of the normal growth of the testes of these animals (Fig. 4) supplies a suggestion as to the reason for their extraordinary response to the maturity principle. These testes grow extremely little until growth in the body is practically completed; and body growth is here extremely rapid relative to that of other laboratory animals (Brody, 1927). From the growth phenomena in both body and testis, therefore, we here have an intimation that during the first two to three months (from egg, not from hatching) of life the anterior pituitary produces *much* growth hormone and very *little* maturity hormone. Quite in agreement with this intimation is the thing we have just observed, namely, that injected maturity extract brings about a phenomenal response in the testis; and we have indications that the injection of growth hormone during the period of most rapid body growth is little able to hasten growth—probably because the food supply (obtained at the will and capacity of regurgitating parents) is then the limiting factor for growth. The curves of testis growth indicate that between the ages of one month and two and one-half months (pigeons) or three months (doves) the testis weight is quite small and practically predictable. It is of course this particular stage of testis immaturity (the flat segments of the curves) that is specially favorable for the testing of maturity hormone preparations.

SIZE CHANGES INDUCED BY PITUITARY HORMONES IN ORGANS OTHER THAN GONADS

Alkaline anterior lobe extracts which were rich in either the growth or the maturity hormone (and with traces at least of the other hormone present), have been found to cause a marked increase in the weight of the thyroids and livers of both doves and pigeons. Mean values obtained from four series of tests on doves (15 birds), with three to eleven daily injections of three different extracts, indicate an increase of 79 per cent in thyroids and 77 per cent in livers. Mean values from three series of such tests on pigons (10 birds), similarly dosed from 2-7 days, indicate an increase of 42 per cent in the thyroids and 73 per cent in the livers. Relatively slight changes occurred in the body weight, and these values essentially represent actual overgrowth as a result of the treatment. The control birds (16 doves; 9 pigeons) were given daily blank injections. Similar effects on these organs did not follow the administration of antuitrin (8 tests), pitocin or pitressin (9 tests) or the luteinizing hormone (14 tests) from pregnant urine (Riddle and Polhemus, 1931).

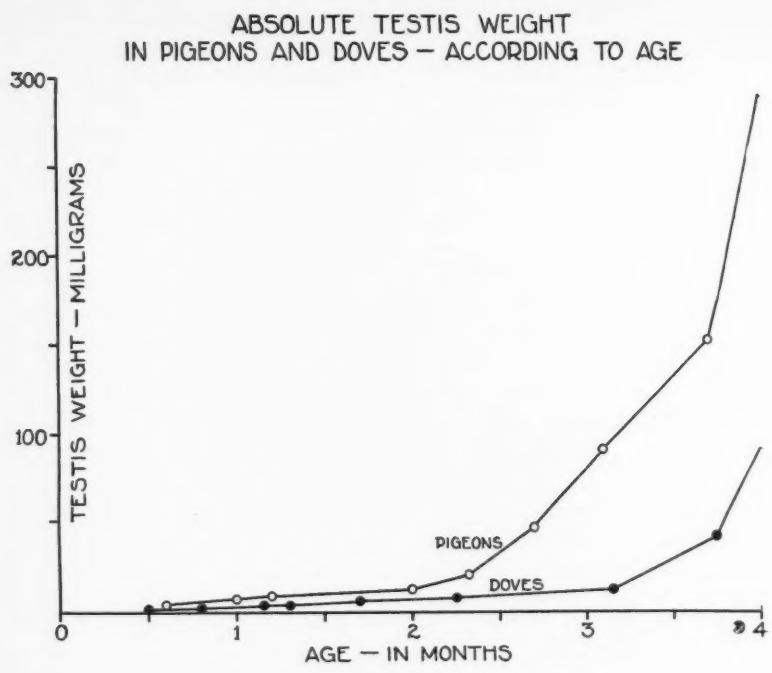

Fig. 4.

The above-mentioned alkaline extracts (made according to the method of Bugbee, Simond and Grimes, 1931; obtained through the courtesy of the Research Laboratory, Parke, Davis and Co.), were not found to cause notable size changes in organs other than thyroids, livers, testes and ovaries during these short periods of treatment. The birds used in these tests were immature (2.3-3.4 months from beginning embryonic development); the response of the thyroid is perhaps to be expected to result from an excess of pituitary stimulation, and the liver enlargement likewise considered as an expression of splanchnomegaly of pituitary origin. The extra growth of testis and ovary is clearly due to the maturity hormone; whether the pituitary is the sole source of this hormone is apparently questioned by some very recent work, particularly by that of Collip (1930) and Claus (1931). The oviducts enlarged under the longer treatments.

ON THE POINT OF ACTION OF THE LUTEINIZING HORMONE IN THE OVARY

Studies on the action of the luteinizing hormone have been confined essentially to mammals, and the general interpretation of the results obtained there is that this hormone stimulates the production of lutein cells in the follicle wall with consequent imprisonment of the ova; ovulation is thought to fail because the wall cannot rupture. Some observations of the action of this hormone on the bird ovary cast much doubt on the accu-

racy or completeness of this interpretation. Without attempting at this time to consider much of the evidence I wish to question this interpretation; and to indicate that in immature bird ovaries the luteinizing hormone from pregnant urine *inhibits growth in the ova* primarily, and often or usually stimulates follicle cell formation. The latter process can here be considered neither the cause of the stoppage of growth in the ova nor a barrier to their liberation.

Fig. 5. Part of ovary of dove, blank injected; control for Fig. 6. The follicular epithelium almost uniformly consists of a single layer of cells.

Figures 5 and 6 give something of the histology of the ovaries of a control dove (70 days after hatching) and of another given five daily injections of luteinizing hormone. It can here be seen that the thickness of

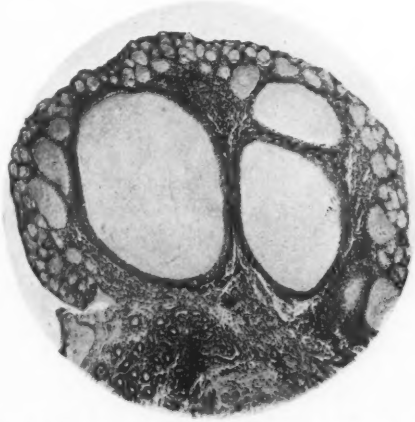

Fig. 6. Part of ovary of dove injected 5 days with luteinizing hormone from pregnant urine. The follicular epithelium is thickened at many, but not all, points of the periphery of the largest ova. Around ova of small or intermediate size this activation of the epithelium is rare.

the follicular epithelium is neither much nor constantly increased by the treatment. It has been possible to show (Riddle and Polhemus, 1931), that growth—which in bird ovaries of this stage is almost wholly a matter of the growth in the larger individual ova—was entirely stopped by this treatment, and that the oviducts of treated birds undergo a definite decrease in size during such treatment. There is the further important consideration that none of the ova thus inhibited could possibly have become ready to ovulate (even if highly stimulated) until more than three weeks later.

Perhaps it is only or especially in mammals, where the mature ovum is so minute—and where even in immature individuals some of the more advanced follicles can mature and rupture after only a day or two of stimulation—that a primary effect on the ova would probably be overlooked.

THE DEVELOPMNET AND FUNCTIONING OF THE CROP-GLAND OF PIGEONS IS CONTROLLED BY AN ANTERIOR PITUITARY HORMONE

It is reasonably clear that the anterior pituitary produces or conditions several apparently quite different phenomena in the body. It is a notable stimulator—stimulating growth, sexual development, thyroid development, adrenal development, lactation, and the bleeding of menstruation; it is probably responsible for certain changes in the water, gaseous, nitrogen and basal metabolism, and doubtless for still other things. No one supposes that each of these changes or reactions is produced by a separate pituitary hormone, though most investigators believe that more than two anterior pituitary hormones are involved. All will agree that the administration of any pituitary fraction should be accompanied by the widest possible search for its various effects. It is in this connection that we here call attention to a newly found and quite remarkable reaction of an anterior pituitary hormone (not yet more definitely identified). The crop-glands of pigeons develop periodically and begin the production of the so-called "crop-milk" precisely at the time their young are hatched. This whole process has been found (Riddle and Braucher, 1931) to be under the control of the anterior lobe of the pituitary.

Some of the particulars may be very briefly summarized. Both male and female doves and pigeons, like some other species of birds, produce a crop-milk which they feed by regurgitation to their newly hatched young. The crop-glands that form this milk are cyclically developed in two dorso-lateral areas of the crop mucosa which, in ordinary life-stages, are not differentiated from the remainder of the crop wall; all of this wall is of paper thinness, and is wholly free of true glandular structures. Only if and when a bird has incubated eggs to nearly full-term do these two areas begin to develop and differentiate into crop-glands. At this time, however, these parts of the crop mucosa exhibit an astonishing proliferation; the cells nearest the crop lumen become loaded with a fatty substance and then free themselves completely from the "gland" surface. These desquamated cells and their loads of a little known fatty material constitute the crop-

milk. Within the glandular area the mucosa increases its thickness by as much as 1500 per cent within the short space of four to five days.

This thickening of the mucosa, with complete milk formation, we have produced at will by the injection of certain anterior lobe extracts; and by such extracts only. This result is thus obtainable entirely apart from any particular phase of the reproductive cycle, at any age, and in birds of either sex; in squabs two weeks old—i. e., in young still receiving crop-milk from their parents—we have established this response and caused them to begin the secretion of their own crop-milk. All of the effective extracts used by us were rich in the maturity hormone, and all probably (some certainly) contained the growth principle, in addition, of course, to other possible anterior pituitary derivatives. Antuitrin and the luteinizing hormone from pregnant urine are ineffective. Pitocin, pitressin, insulin, adrenalin, thyroxin, folliculin, and several other tissue derivatives are likewise ineffective. The effective crop-gland stimulant is destroyed by heat.

We do not suppose that a special or new hormone is involved in this control of the crop-gland, but consider this a hitherto unknown activation by the gonad-stimulating or (and ?) by the growth hormone. If this reaction should prove to be a response to the growth hormone it would provide by far the best and quickest test now available for that hormone; the effect is macroscopically observable (without killing the bird) as early as 72 hours after injecting the first of three daily doses. The full effect of the extract is obtained after complete section of the nerve supply to the crop.

This case provides additional evidence (Riddle, 1927, 1929) of the significant extent to which the rhythmic processes of reproduction transcend neural regulation and are endocrine controlled.

SUMMARY

The special suitability of the immature dove or pigeon testis as a test object for extracts containing the maturity principle of the pituitary is shown and figured. The test is most accurately made in birds one to two months after hatching. Curves showing the unusual character of testis growth in doves and pigeons are given.

Alkaline extracts of the anterior pituitary, as prepared by Bugbee, Simond and Grimes (1931) for either growth or maturity principles (and probably both of these are always present), produce a marked increase in the weight of the thyroids, livers and gonads of immature doves and pigeons. The luteinizing hormone from pregnant urine does none of these things. It seems probable that the enlargement of thyroids and livers, like that of the gonads, is a true effect of anterior lobe hormones.

The action of luteinizing hormone from pregnant urine on the bird ovary is probably primarily an inhibition of growth in the ova; secondarily and irregularly a thickening of the follicular epithelium usually occurs. The accuracy of the current interpretation (obtained from studies on mammalian ovaries), of ova imprisoned by the stimulated formation of lutein cells, is questioned.

Some aspects of a newly found control of the secretion of "crop-milk" in pigeons by an anterior lobe hormone are considered. It is thought that a hitherto unknown hormone is not involved, but that this extraordinary reaction probably is produced by the maturity or (and ?) the growth principle. If the growth hormone should prove to be solely involved this crop-gland response is the easiest and speediest known test for that hormone.

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PLACENTAL HORMONES*

J. B. COLLIP, D. L. THOMSON, J. S. L. BROWNE, M. K. McPHAIL AND J. E. WILLIAMSON

McGill University

MONTREAL

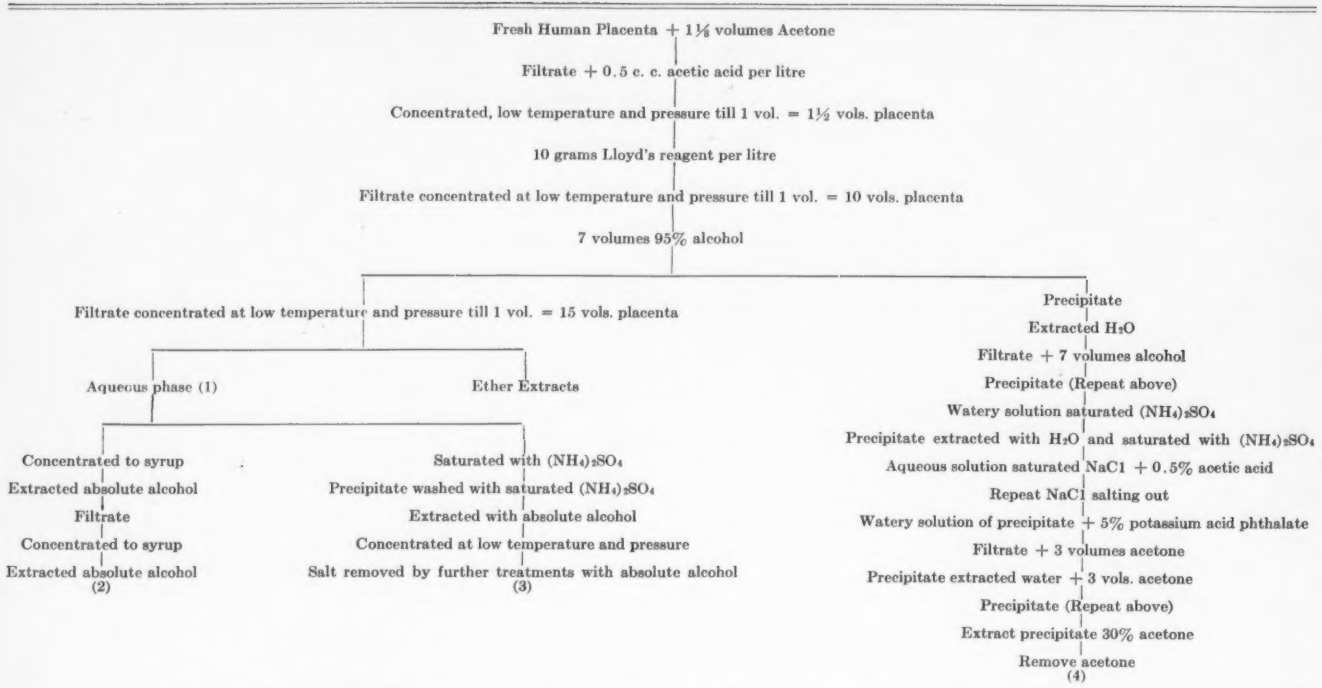
Since an extensive review of the literature on this subject has been given in earlier communications (3, 4), we propose to give in this paper only a brief account of the methods which we have used and of the results which we have obtained in our studies on the placental hormones.

Human placentae have been used as a source of raw material since no satisfactory results could be obtained by using placentae of the dog, rabbit, rat, pig or cow. The methods employed in the extraction and subsequent fractionation of the human tissue are shown in Chart I. The emmenin fraction at stage 1 has been widely used for physiological experiments and in clinical studies, but can be further purified by alternative methods to yield products 2 and 3. Emmenin is probably of the greatest interest because it would appear to be a hitherto unrecognized active principle of placental origin. There still remains much to be learned about the chemistry of this active principle and of its relationship to the other known oestrogenic hormones, "Theelin" and "Theelol" (7). Work now in progress along these lines in our laboratory is as yet not sufficiently advanced to allow one to make dogmatic statements relating to this aspect of the subject at the present moment.

Physiologically, emmenin may be characterized as follows: The oral administration of the active extract to immature rats, nineteen to twenty-one days of age, in small amounts, for three days, results in the appearance of oestrus in from three to five days. The minimum amount so fed which consistently produces this effect we have termed the oral day unit. Examination of the ovaries of animals in which oestrus has thus been induced does not reveal any marked change. At times a slight increase in follicular development may be noted, but there is no consistent increase in weight of the ovarian tissue. Continued daily administration of one to three day units to immature rats may result in the appearance at slightly irregular intervals of oestrus vaginal smears. Continued administration of larger doses (10 units) has resulted, as a rule, in the manifestation of a continuous oestrus vaginal reaction until the age of normal puberty has been reached, after which time normal cycles have occurred.

The cycles of normal adult animals have been unaffected by the continuous daily administration of ten or more units. Similarly, no interference with the normal processes of pregnancy or lactation has been ob-

*Read before the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, June 9, 1931.


Fresh Human Placenta + 1½ volumes Acetone
Filtrate + 0.5 c. c. acetic acid per litre
Concentrated, low temperature and pressure till 1 vol. = 1½ vols. placenta
10 grams Lloyd's reagent per litre
Filtrate concentrated at low temperature and pressure till 1 vol. = 10 vols. placenta
7 volumes 95% alcohol
Filtrate concentrated at low temperature and pressure till 1 vol. = 15 vols. placenta
Aqueous phase (1)
Ether Extracts
Concentrated to syrup
Extracted absolute alcohol
Filtrate
Concentrated to syrup
Extracted absolute alcohol
(2)
Saturated with (NH4)2SO4
Precipitate washed with saturated (NH4)2SO4
Extracted with absolute alcohol
Concentrated at low temperature and pressure
Salt removed by further treatments with absolute alcohol
(3)
Precipitate
Extracted H2O
Filtrate + 7 volumes alcohol
Precipitate (Repeat above)
Watery solution saturated (NH4)2SO4
Precipitate extracted with H2O and saturated with (NH4)2SO4
Aqueous solution saturated NaCl + 0.5% acetic acid
Repeat NaCl salting out
Watery solution of precipitate + 5% potassium acid phthalate
Filtrate + 3 volumes acetone
Precipitate extracted water + 3 vols. acetone
Precipitate (Repeat above)
Extract precipitate 30% acetone
Remove acetone
(4)

served. In no instance has there been any evidence of the formation of corpora lutea as a direct result of emmenin treatment nor has true hypertrophy of the ovaries been observed at any time.

The extract is without effect on adult castrates, unless very large doses are given. We attribute this latter effect to traces of oestrin which have not been removed from our extracts. The oestrogenic effects of emmenin are due, we feel, to activation of the ovaries to the liberation of the oestrogenic ovarian hormone. We have obtained evidence by implantation of the ovaries of immature rats into adult castrates that such ovaries contain the oestrogenic hormone.

The production of an oestrus vaginal reaction in immature rats, as in the assay of extracts containing emmenin, does not shorten the time of appearance of normal puberty and maturity. In fact, in some instances spontaneous puberty may actually be delayed a few days in such animals.

No effects have been observed in either young or mature male rats treated with extracts of emmenin.

The physiological effects of the second principle which we have obtained from human placenta in the form of purified extract of protein-like substance shown in the chart as No. 4 have been extensively investigated (5) and the results may be summarized as follows:

Assay: Immature rats nineteen to twenty-one days of age injected subcutaneously daily for three days with the purified extract manifest oestrus on the third to the fifth day. The minimum amount so injected which consistently produces this effect we term the day unit. Both gross and microscopic examination of the ovaries of immature animals which have been injected with varying doses of the active extract for varying periods of time have been made and the results obtained are of great interest. Dosage which is just sufficient to induce the oestrus vaginal reaction has very little effect upon the ovaries. They may show an increase in weight over that of the controls of three or four milligrams, and in section show a slightly increased development of a few follicles. When the amount of extract administered is doubled or trebled, the ovaries removed on the fifth or sixth day have a vastly different appearance. They correspond very closely with the ovaries of unmated animals shortly after the appearance of spontaneous maturity. Normal young corpora lutea are present and also healthy follicles in the course of maturation.

Continued daily administration of from three to twenty units to immature female rats has resulted in the appearance of a succession of normal cycles at four or five day intervals. Even after some weeks of such treatment the ovaries on examination have been found to correspond with those of normal adults. Treatment with this hormone has resulted in the rapid production of ovaries similar in appearance to those of the normal adult. A point of considerable significance is the fact that the growth of the ovaries, though rapid at first, does not go beyond normal adult size.

Normal adult female rats which have been injected daily with moderate amounts (five to twenty units) have shown occasional slight irregularities of the cycles. They have mated successfully while under such treatment and have produced and reared normal size litters in the usual time. No hypertrophy of the ovaries has been noted in such animals.

The active principle of this extract may be presumed to be of protein nature. It is thermolabile and also ineffective by the oral route in doses up to 25 units.

Effect on Males: Continued daily injections of from two to twenty units of this active principle into adult normal male rats has produced with remarkable uniformity marked enlargement of the accessory genital tract structures, especially of the seminal vesicles and prostate gland. Further, an increased rate of growth of these structures has been observed in immature males injected with the hormone. These effects are quite comparable to those which should theoretically be produced by large doses of the male hormone, judging by its action in castrates. A point of some interest in these experiments is the relatively small effect on the weight of the testes as compared with that of the seminal vesicles and prostate gland. Thus the latter may show, as in one experiment, after one month's treatment, an increase in size of 342 per cent as compared with an increase of only 24 per cent in the testes weight. It may be concluded that this principle stimulates the male gonad to work rather than to grow.

Effect of Emmenin and the Second Principle Administered Simultaneously: It was pointed out above that continued administration to young animals of emmenin in 10 unit doses daily resulted in the manifestation of a continuous oestrus vaginal reaction. It has been found that simultaneous treatment with the second principle results in the breaking of the continued oestrus reaction. Recently we have treated young adult females with both principles, emmenin being given by the oral route and the second principle by injection. After 10 units of emmenin were administered along with 20 units of the second principle, the cycles were broken and a prolonged period of dioestrus resulted. The ovaries, after three weeks of such treatment, were found to be extensively luteinized and greatly enlarged (197 mgm. to 347 mgm. in weight).

It should be emphasized that such interference with the cycles, such ovarian luteinization and hypertrophy, has never been obtained by us with either of these two principles, given singly, in these dosages.

These latter results are of the greatest significance because they establish the inter-relationship of function of the two principles. Also, we have demonstrated the fact that, judged by the response of the rat, it is possible to obtain, in chronic rather than acute experiments, comparable results by the injection either of adequate amounts of the two placental principles, or ether-extracted pregnancy urine, or by repeated pituitary implantations.

It may be added here that we have prepared from pregnancy urine, by the methods used in dealing with placenta, two extracts which seem to correspond with our emmenin and the second principle as obtained from placenta.

DISCUSSION

Since the pioneer work of Aschheim and Zondek (12) and of Smith and Engle (9) on the effects of implants of pituitary substances, a great mass of literature has appeared upon this subject and various direct developments therefrom. It is a matter of extreme difficulty, if indeed it is not an impossibility, adequately to assay and blend the various results of various workers in this field. It is therefore with the desire to correlate the work of our own laboratory with that of others that the following discussion has been introduced.

No one who has injected rats with ether-extracted pregnancy urine for a period of weeks and who has also seen the effects of repeated homoimplants of pituitary substance upon the ovaries, can doubt the similarity of the ultimate results in so far as the genital tract is concerned. It is therefore most logical that it should have been assumed by most workers that the pituitary-like effects of pregnancy urine are due to true pituitary hormones contained therein.

Now in the case of our own earlier work with placental extracts, the inability which we experienced to duplicate with our extracts the results which can be obtained so readily with pituitary implants or with pregnancy urine led us to doubt the identity of the placental and anterior pituitary hormones. We were then dealing almost entirely with the emmenin fraction and our doubts were increased when we found ourselves unable to prepare, by similar methods, active extracts from fresh or frozen pituitary glands. The uniform response following oral administration of the emmenin fraction made it most improbable that the active principle here concerned was to be found in the pituitary gland. Today we still feel that in the case of emmenin we are dealing with a product which is non-pituitary in type and which is probably a true placental hormone.

Later, after we had been successful in purifying the second principle to a considerable degree, and had had an opportunity of studying the physiological effects of this extract, it was again apparent that whereas there was a much closer parallelism between the effects of this latter principle and of pituitary implants, or of pregnancy urine injections, than in the case of emmenin, there was still a considerable difference between the effects of the second principle and those of either pituitary implants or of pregnancy urine.

Our recent work, in which a combination of emmenin and our second principle has been shown to produce massive luteinized ovaries in young adult rats, calls for a re-examination of the theory.

Zondek (13) on the basis of indirect evidence has proven that pregnancy urine contains two ovary-stimulating hormones which he dis-

tinguishes as Prolan A and Prolan B. The former has been obtained free from the latter in certain urines of non-pregnant women, and it has been associated with the presence of endocrine disorders—tumours and inflammatory lesions—or the menopause, and is responsible for the non-specific reactions seen in the Aschheim-Zondek pregnancy test (Reaction 1). Prolan B is represented as the luteinizing hormone. Both are precipitated by alcohol. Wiesner (11) has likewise in his Rho theory adopted a somewhat similar point of view. Extracts of pregnancy urine containing an alcohol-insoluble ovary-stimulating hormone have been prepared by various workers. The physiological effects of such extracts as prepared by Dickens (6), van Dyke and Wallen-Lawrence (10), and also by ourselves, correspond very closely with the effects which we have described as characterizing our second principle.

Recently Fevold, Hisaw and Leonard (8) have reported on the preparation of active extracts of desiccated anterior pituitary lobes. Following the initial use of 50 per cent pyridine, they have prepared two fractions—both alcohol insoluble—one of which would appear to correspond somewhat in its physiological reactions to our second placental principle, on the one hand, and to the extracts of pregnancy urine referred to above, on the other. The second fraction which these latter authors have described has been found to be without appreciable effect by itself in immature rats, but when combined with the first it causes massive luteinized ovaries to develop in the course of a few days.

A careful survey of the published work of many investigators, with the possible exception of that of Claus (2), fails to give convincing evidence that there is such an entity as a specific luteinizing hormone. Our own work has likewise raised the same doubt in our minds. Luteinization associated with ovarian hypertrophy and an acyclic vaginal reaction is more probably the end result of the combined action of two or more separate principles. The work of Fevold, Hisaw and Leonard (8) on pituitary extracts, and our own on placental products, justify such a viewpoint.

The question of the identity in each case of an active principle which is alcohol-insoluble and which has been obtained from pituitary glands, from pregnancy urine and from placenta, cannot be answered at this time. We feel that the source of the active principles found in pregnancy urine is the placenta. One of these principles presents a certain degree of parallelism in its physiological effects with certain anterior lobe extracts. Emmenin cannot, however, be related to any known pituitary hormone.

An important problem in the physiology of oestrus, on which our recent experiments have a bearing, is that of the origin of the cyclic nature of the phenomenon. To this there are, as in the case of the analogous problem in cardiac physiology, several theoretically possible solutions. In the first place, it might be supposed that the rhythmicity is inherent in the anterior pituitary itself, or is imposed upon it from some

higher, unknown controlling organ; that the gonad-stimulating substance is liberated rapidly just before oestrus, and slowly if at all just after oestrus. Existing experimental evidence does suggest that the hormone content of the anterior pituitary is high before oestrus, and low immediately thereafter; whence it follows, if this theory is accepted, that the rate of secretion is a function of the concentration of hormone in the organ, and is in fact, an expression of the rate of production. This solution of the problem, however, leaves us confronted with the still more difficult question: What makes the anterior pituitary itself cyclic?

The second hypothesis, a modification of the first, avoids this difficulty. It postulates an alternation of endocrine activity between pituitary and ovary. The gonad-stimulating hormone evokes in the ovary not merely follicular maturation, but an outpouring of oestrin; oestrin, in the well-founded view of Moore, Hisaw and others, inhibits secretion of the gonad-stimulating hormone, so that the ovary might again come to rest. In view of the experimental evidence already alluded to, that the hormone content of the anterior pituitary is decreasing at the time when the body is being flooded with oestrin, it appears that, if this hypothesis is accepted, the action of oestrin is to inhibit the production of the pituitary hormone, rather than to inhibit the escape of preformed hormone from the gland. It will be seen that a salient feature of this very attractive hypothesis is the supposition of sufficient latent periods: there must be some delay before the oestrin, evoked by the pituitary, has time to act and inhibit the pituitary; and some delay, after the flood of oestrin, before the pituitary is able to resume full activity.

There remains a third hypothesis. Disregarding, as a separate problem, the probability that there are fluctuations in the hormone content of the anterior pituitary, it is possible to assume that the secretion of the gonad-stimulating hormone therefrom takes place at an approximately constant rate, but that the ovary, having once responded in its characteristic manner, passes into a refractory state, whence it at length spontaneously emerges to respond anew to the continuous stimulus by a second cycle, and so forth. That the ovary does in fact possess some such property is indicated by our studies of the anterior-pituitary-like substance of the placenta. Not only do daily injections of large doses of this substance fail to interfere markedly with the oestrus rhythm of adult female rats, but in immature rats, whose pituitaries are presumably still dormant, they produce, before the time at which spontaneous puberty should appear, a succession of apparently normal cycles. We are not aware that any other anterior-pituitary-like substance has been shown to have this property; thus Zondek reports that his alcohol-insoluble Prolan A, like our alcohol-soluble emmenin, produces continuous oestrus when injected daily into immature rats. But unless it is supposed that our preparation is not truly anterior-pituitary-like, but is rather a pituitary stimulant, as Evans has recently suggested for Prolan, then we have shown that the ovary may

respond in a cyclic manner to a practically continuous stimulus, and that this third hypothesis is not to be lightly set aside. It is not improbable, however, that, in fact, the mechanism is too complex to be expressed in hypotheses as simple as these; the truth may lie in some combination of them, in which the possibly diphasic activity of the anterior pituitary may play its part.

CLINICAL USE OF THE TWO PLACENTAL PRINCIPLES

Campbell and Collip have elsewhere (1) reported on the clinical use of preparations of emmenin and the second, anterior-pituitary-like, principle of the human placenta. The observations which have thus far been made may be summarized as follows:

Emmenin:

Dosage: Five cc. doses have been administered orally one to three times daily before meals. Each cubic centimeter of the preparation used represented 5 day rat units. It was practically oestrin-free and also free of the second principle.

Results: Over two hundred selected subjects in whom pelvic disease has been eliminated as an etiological factor have been treated and the following impressions have been formed:

(1) In *dysmenorrhoea* excellent results in over ninety per cent of the cases have been observed.

(2) *Oligomenorrhoea*—The majority of subjects of the oligomenorrhoea type of secondary amenorrhoea appear to respond very satisfactorily to treatment, whereas subjects of primary amenorrhoea or of secondary amenorrhoea of some years' duration appear not to be amenable to this therapy. The dosage used in this group of cases has been 25 grams of placenta 3 times daily until results have been obtained or treatment has been discontinued. The average time of 23 days elapsed before menstruation occurred in a group of 40 cases.

(3) *Polymenorrhoea*—In a small series (8 cases) the interval was increased from four to seven days.

The Anterior-Pituitary-Like Principle:

Dosage: A stable preparation of this hormone containing 40 day rat units per cubic centimeter has been administered subcutaneously in from one to two cc. doses daily or bi-daily.

Results: In a series of 40 cases of menorrhagia and metrorrhagia the excessive uterine bleeding has as a rule been controlled. In most instances normal periods have been instituted thereafter, but these have not been of the same regularity as in cases of other types treated with emmenin.

Judging from our recent laboratory findings following the simultaneous administration of both principles, it would appear that clinical studies should be extended along these lines.

SUMMARY

Acetone extracts of human placenta contain at least two active substances apart from ether-soluble oestrin. The alcohol-soluble fraction, emmenin, is active orally and causes premature oestrus in immature female rats; in moderate doses it has no action on the oestrus cycles or ovarian weight of adult female rats, and no action upon males and castrates. The alcohol-insoluble fraction is not active by oral route; in immature female rats it causes premature oestrus with growth of the ovaries to normal adult size; in males it promotes growth of the prostate and seminal vesicles. Simultaneous administration of the two fractions in female rats causes hypertrophy and lutenization of the ovaries with suppression of the oestrus cycles. The methods of purification and the clinical application of these fractions are briefly discussed.

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VARIATIONS IN THE SUSCEPTIBILITY OF THE ALBINO RAT TO TETANIA PARATHYROPRIVA

MARGARET M. HOSKINS
Department of Anatomy, New York University
NEW YORK

It appears from the work of various writers that removal of the parathyroid from the albino rat is sometimes, but not always, followed by fatal tetany. The precentage of deaths reported varies considerably, and satisfactory reasons for this variation have been wanting. It is the purpose of this paper to analyze a considerable series of operations, and present evidence concerning the importance of some factors which have influenced the proportion of fatalities in certain groups of rats. The factors to be considered are as follows: the age and weight of the animals, the season at which the operation was performed, and finally the state of activity of the thyroid at the time of the operation. The first three of these factors have been discussed by Hammett in his series of papers on the thyroparathyroid apparatus: all of them have been considered by the author in preliminary reports made at meetings of the American Association of Anatomists. Now that the series of operations has been extended, the data are offered in the hope that they may be of assistance to other workers in this field.

Hammett (1927) found that in his series age, weight, and season affect susceptibility to tetania parathyropriva as follows: Rats are more susceptible at 65 days (before puberty) than at 100 days when sexual maturity is fully established. The mortality drops from 54 per cent at 60 days to 9 per cent at 100 days. The average initial body weight of the animals which survive is, according to Hammett's tabulation, slightly greater than that of those which die within three days after the operation. In regard to the effect of season he calls attention to a marked rise in susceptibility during March and April. In these months, judging by his graph, the mortality is about 35 per cent. In July it rises to 60 per cent, the highest figure given in the tabulation. In November, the mortality is only 15 per cent. Hammett makes no statement as to whether age and weight were considered in the compilation of the month-by-month records, but one assumes that all other influencing factors were balanced. If this is so, the chart indicates that the Spring rise in mortality is merely a stage in the greater rise to the Summer figure.

The results obtained from our series differ in some respects from those given by Hammett. The points of difference will be taken up as the factors are discussed.

MATERIAL AND METHODS

The data presented include the results of some operations performed by Dr. S. B. Chandler, Dr. M. D. Overholser, Mr. J. A. Rosof, and Mr. J.

F. Thackston, as well as those done by the author. Some were performed at the Medical School of the University of Arkansas, and the rest in New York University. The period of time covered is about eight years. A general picture is thus presented, rather than the more limited one afforded by a study of parathyroidectomy in rats of one colony. Variations which might be due to differences in diet or minor differences in technique have been carefully considered, but comparisons among the individual groups have shown them to be negligible.

The technique of the operation has been fully described by Overholser (1929) and needs no further discussion. It was originally learned from Hammett, by the author, and passed on by her to the other workers mentioned above.

The material used for microscopic study was fixed in Bouin's fluid, embedded in paraffin and sectioned (usually at 10 μ). Slides were stained with hematoxylin and eosin.

Those who have attempted work involving parathyroidectomy are probably familiar with the criticism made of such studies: it is frequently said that the results are vitiated by the presence in many animals of accessory parathyroid bodies. In this series of operations a careful search has been made for such accessory parathyroid tissue. Serial sections of the neck region anterior to the vertebrae have been thoroughly examined. Throughout the course of the work it has been found that from five to seven per cent of the animals have accessory parathyroids (Hoskins and Chandler, 1925; Overholser, 1929). Occasionally, however, a strain of rats may be found in which the number rises to 20 per cent. Such a group was obtained from the University of Pittsburgh. This colony, originally derived from Wistar Institute Stock, was used twice, the samples being tested about a year apart and both showing this high percentage of accessories. It is interesting to note that the tendency towards diffusion of the parathyroid tissue runs, apparently, in families of rats. The fact has emphasized the necessity of continuing the rather tedious process of looking for accessory parathyroids, especially when new stock is being used. In the present study the check has been made in every survivor, except those which lived long enough to show the breaking down of the teeth, which is a reliable criterion of absence of parathyroid tissue in the rat. The series is, therefore, presented with complete assurance that the results are not distorted by the accidental inclusion of any incomplete operations.

MODIFYING FACTORS

Effect of Age: With regard to the effect of age on the susceptibility of rats to tetania parathyropriva, the present paper has nothing to add to the conclusions published by Hammett (1927) and Overholser (1929). The number of our operations performed at 90 days of age is not large, but they indicate a marked lowering of susceptibility following puberty. The figures from the two series are as follows: 60 days, 171 animals, 52 per cent tetany; 90 days, 53 animals, 37 per cent tetany. If two groups

are selected in which the factors of weight and season are the same, an even greater difference between the two ages is shown: 60 days, 32 animals, 56 per cent tetany; 90 days, 27 animals, 13 per cent tetany.

Weight and Season: The study of the effect of differences of weight and season on the susceptibility to tetany is based entirely on operations on animals of approximately 60 days of age, since this series affords the greatest amount of material. The results of 171 operations are summarized in Table I which shows their grouping according to the weight of the animals and the season at which the operation was performed. The weight in each case is considered in its relation to the figure given in "The Rat" (Donaldson, 1924) as normal for the sex and exact age of the animal. For example, operation number 10 was done on a male rat, 57 days old, weighing 126 grams. The normal weight of a male rat of this age is 74 grams. The weight of this one is accordingly entered in the records as +52 grams. In this way differences between the sexes and slight variations in age are taken into account in establishing the norm. A divergence of 20 grams above and below the Wistar norm is considered insignificant, as it corresponds with the standard deviation of the weight in the series. Cases having weights above and below this range are classed respectively as overweight and underweight.

The figures in the box at the lower right-hand corner of the table summarize the whole series: 171 animals of which 52 per cent died of tetany within two days after the operation. The series extends over a considerable period of time, and includes operations done under slightly different conditions of diet and climate on rats from various colonies. It is, therefore, interesting to compare the figure of 52 per cent with the average mortality in different homogeneous groups. The records of 90 operations have been arranged in 15 groups, each group being composed of 6 litter mates. The environment of the members of each group was, of course, the same. The average mortality, by groups, is 57 per cent. No differences existing among the groups can be traced to environmental factors, except in cases where poor conditions have produced rats which are definitely sickly. Our conclusion is that under normal conditions one may expect three or four animals out of a litter of 6 to survive parathyroidectomy. Small fluctuations of this mortality rate are to be expected, but if all the members of a litter die or survive, one is justified in believing some unusual condition to be present.

Turning now to the effect of body weight on susceptibility, as shown in Table I, the impression is given that susceptibility to varies inversely with weight. The cases are summarized under this head in the right-hand column, and are as follows: normal weight, 58 per cent; underweight, 74 per cent; overweight, 37 per cent. A similar difference between the weight-groups is shown also in any one season, though it is most marked in the Summer series. It will be shown below, however, that the greater immunity to tetany of the overweight animals in this series was not actually

due to their superiority in size alone. A considerable proportion of them were found to have a condition of the thyroid which is correlated with complete absence of tetany. The inclusion of these rats in the series distorts the figures obtained from a study based on weight alone, and gives a false idea of the importance of the weight factor. A more accurate estimate is given by the figures in *brackets* in the right-hand column of Table III. Here we have eliminated the influence of thyroid activity as well as that of season. The figures are: normal, 53 per cent; overweight, 59 per cent; underweight (only three cases), 100 per cent.

The data on the relation between weight and susceptibility to tetany may be summarized as follows: rats which are more than twenty grams below the normal weight for their age exhibit abnormally great susceptibility. Those within twenty grams above and below the normal figure, and those which are considerably overweight have a mortality between 50 and 60 per cent. This is in general agreement with Hammett's conclusion that the animals which die of tetany have an average weight below that of the surviving group. The facts are presented in a form which enables us to set more definite limits to the effect of variations in weight. It appears that among normally healthy animals weight *per se* is not an important factor in susceptibility. The underweight group consists, obviously, of subnormal rats; and it is quite to be expected that they should suffer more than normal animals from any operation.

Seasonal Variation: The data on seasonal variation in susceptibility are also summarized in Table I. Three divisions of the year are used.

	Winter			Spring			Summer			Totals by Weight		
	No	Wt	%Tet	No	Wt	%Tet	No	Wt	%Tet	No	Wt	%Tet
N+	47	+38	43%T	3	+30	33%T	16	+33	6%T*	66	+37	33%T*
N	32	+7	56%T	19	-3	76%T	27	-4	56%T	78	+1	58%T
N-	8	-35	75%T	3	-34	66%T	16	-35	81%T	27	-35	78%T
Totals by Season.	87	+20	51%T	25	-3	72%T	59	+1	51%T	171	+10	52%T

*Figures in this group distorted by the inclusion of hyperthyroid animals.

Winter includes the months from September through March; Spring, April and early May; Summer, late May to September. This division has been used except in the case of some operations performed early in May in Arkansas. These were classed as Summer operations, since Summer temperatures prevail in that locality from April through October. The fig-

ures, summarized at the bottom of the table, do not show the seasonal variation which was expected. According to Hammett, and also on the basis of the results of our first experiments, a marked rise in susceptibility is to be expected in Spring and Summer; but in the entire series no such increase occurred. In both Winter and Summer the mortality was 51 per cent. There was an increase to 72 per cent in the Spring, but examination of our records suggests that this was due to the inclusion of a number of animals suffering from a digestive disturbance.

As in the case of the data on body weight we should exclude from a consideration of seasonal variation those animals in which the thyroid is hyperactive; and, in view of the conclusion that underweight animals are abnormally susceptible to tetany, such cases should also be eliminated from the count. Unfortunately the material from the Spring series could not be accurately tested with regard to thyroid activity, so that a comparison can be made only between Winter and Summer cases. Selecting animals of normal weight, in which the thyroid was normal, we have 18 cases in Winter, with 50 per cent tetany, and 15 cases in Summer with 60 per cent tetany. In groups of this size the difference between 50 and 60 per cent tetany is negligible. From the data collected it seems, therefore, that differences in season do not, alone, produce variations in susceptibility to tetany. They may be secondarily responsible for such variations. For example, in Overholser's series (1929) a group of rats operated upon in July showed a very high mortality, and the same condition was found in our Arkansas Summer series. But a very large proportion of the animals of these two groups were underweight and sickly. It has been our experience that colonies fall off in weight and vigor during hot weather, and we believe that if such ill effects of the climate can be overcome, rats will be found to survive parathyroidectomy as well in Summer as in Winter.

Thyroid Activity: It is evident from the preceding sections that no satisfactory explanation of lowered susceptibility to tetania parathyreopriva can be based on the factors of weight and season. It can be said that poor general health, of which low weight is a symptom, predisposes the animals towards tetany; but among healthy rats the mortality was 50 to 60 per cent, and no condition has been found heretofore which could be correlated with complete immunity to tetany. The best known experiments in this direction are, perhaps, those which Hammett has reported. In his series the mortality among rats which had been gentled was only 12 per cent, while 78 per cent of the control animals from the Wistar stock colony died of tetany. He attributes the low mortality to the relaxation of muscle tonus effected by gentling. We have made some attempts to repeat this experiment, but have been unable to correlate susceptibility with nervous condition. A series of wild gray rats caught in wire traps and brought to the laboratory in a condition of extreme excitement yielded only one case of tetany out of fifty operations, and we have not succeeded in lowering postoperative mortality by gentling our animals. In any case,

the factor of nervous condition may be ruled out of the present series, as no animals are included which had been gentled. They were all tame enough to be handled easily, but none were more relaxed than those we secured from the Wistar stock, among which Hammett himself found a mortality rate of 78 per cent. The low mortality of certain groups in our series may, however, be explained by reference to the condition of the thyroids of some of the animals, at the time the operations were performed. The most striking of these groups is the Summer overweight, in which the mortality fell from the expected 50-60 per cent to only 6 per cent. This group included nine animals sent directly from the Wistar Institute (ordinary stock) to the Biological Laboratory at Salisbury Cove, Maine, and five from the same source sent to Ohio State University. The plan for the experiment was to test the effect of temperature on susceptibility by comparing the results of operations performed in the same season but under different climatic conditions. The experiment was unsuccessful, since no one of the rats died, either in the heat of Columbus or the coolness of Maine. We had on record no other homogeneous group of fourteen rats in which there were no fatalities, and a search for the reason for their immunity to tetany was clearly desirable. The obvious place to look for a variation from the normal was in the parathyroids themselves, and since it is our custom to preserve and section the tissues removed at operation, this material was readily available. The parathyroids appeared to be perfectly normal. In looking over the material, however, our attention was attracted by the condition of the thyroids of these subjects. Each removed piece consists of the parathyroid plus a small sample of thyroid, since the latter gland partially surrounds the former and must be cut into to insure complete parathyroidectomy. The material gives, therefore, opportunity to judge of the condition of the thyroid of the animal at the time the operation was performed. In these fourteen cases, it was evident that the gland had been hyperactive. The follicles were all lined with tall columnar cells, staining but faintly with eosin. The lumen of each follicle was small, and contained little or no stainable colloid.

Adopting the working hypothesis that the immunity of these animals to tetany was connected with their hyperthyroidism, an examination of other material from operations was undertaken. The next group to be studied was the Winter overweight series, in which the mortality was slightly lower than usual (43 per cent). In this group, four samples of thyroids were found which were readily recognized as active. These animals were not Wistar rats. The exclusion of these four cases from the group raised the mortality rate to the normal figure of 50 per cent.

The idea that immunity to the effects of parathyroid removal depends mainly on the activity of the thyroid was, of course, obvious and tempting. It was found, however, that the condition of the thyroid could not be accurately determined by simple inspection. The eighteen cases already found were clear enough, and further search among the slides added one more

obviously active gland to the list. But except for these instances it was impossible to grade the thyroid material with any degree of certainty. In most cases, some follicles could be found lined with tall columnar epithelium, but others were formed of flattened cells, and the intermediate conditions were always present. It was, therefore, necessary to use some method susceptible to mathematical analysis. The following technique was adopted: Ten sections were drawn with a camera lucida from each sample of thyroid studied. In each section the outer margin of a group of follicles was traced, and then the inner margin of the epithelium of each follicle was outlined. The sketch thus gave a complete outline of the epithelial tissue of the field represented. The ten drawings of each gland were cut out with fine scissors, separating the part which represented epithelium from that which represented colloid or empty lumina. The parts were then weighed, and the proportion of the gland which consisted of epithelium thus determined. For example:

Weight of paper representing epithelium.....	4.5 gr.
Weight of paper representing lumina.....	1.9 gr.
Total weight	6.4 gr.
Epithelium	70% of gland.

This figure may be regarded as a fair index of the activity of the thyroid in question. It is generally accepted that thyroids in which the follicles contain much colloid and are lined with flat cells are less active than those in which the epithelium is columnar and the lumina are small. The ratio of epithelium to total area in sections is not, of course, a precise index of the physiological condition of the gland, since it takes no account of the density of the colloid. It is also quite possible that cells of medium size are not all in the same state of activity. The method gives, however, a rough estimate of the condition, and is thought to be valid so long as emphasis on minute variations is avoided. It is, at least, more satisfactory than simple inspection.

The figures obtained in the manner just described were first studied to determine whether the index of thyroid activity is higher in surviving rats than in those which die of tetany. The results are shown in Table II.

	No.	Thyroid Index M.	S. D.	P. E. M.	Comparison
All cases.....	45	71%	±10		
Tetany.....	23	67%	± 8.3	±1.2	$M_1-M_2=6\pm2$
No tetany.....	22	73%	±10.3	±1.6	

Forty-five cases are divided into two groups; twenty-two no tetany, and twenty-three fatal tetany. The average thyroid index of the survivors was 73 per cent, that of the animals which died 67 per cent. The difference

of 6 per cent between the two groups has a probable error of ± 2, giving a probability of 20:1 that it is significant.

A more interesting result is seen when the figures are grouped as in Table III. This is planned to show the percentage of tetany occurring in

	Below S. D.				M± S. D.				Above S. D.				Totals by Weight			
	No.	Wt.	Thyr.	% T	No.	Wt.	Thyr.	% T	No.	Wt.	Thyr.	% T	No.	Wt.	Thyr.	% T
N+	7	+30	56	71	10	+35	70	50	5	+48	87	0	22 **17**	+36 **+33**	69 **61**	45 **59**
N	3	+11	58	33	14	+8	71	57	1	—11	82	0	18 **17**	+7 **+8**	69 **68**	50 **53**
N—					3	—31	74	100	2	—48	90	0	5 **3**	—38 **—31**	80 **74**	60 **100**
Totals by Thyroid Index	10	+24	56	60	27	+12	71	59	8	+19	86	0	45 **37**	+15 **+15**	71 **65**	50 **59**

animals with normal, hyperactive and hypoactive thyroids respectively. The mean thyroid index of all 45 cases was 71 per cent, with a standard deviation of ± 10. Thyroids with an index between 61 per cent and 81 per cent are classed as normal, those above 81 per cent as hyperactive, and those below 61 per cent as hypoactive. The three groups are still further subdivided according to weight, to facilitate comparison with Table I. All cases are from the Winter series; hence seasonal variations, if they exist, are excluded. The figures in the summary by thyroid index are as follows: Hypoactive thyroid, 60 per cent tetany; normal thyroid, 59 per cent tetany; hyperactive thyroid, no tetany. The complete absence of tetany in the hyperactive group is a striking fact, especially when it is noted that two of these animals belong in the underweight group which ordinarily exhibits a high susceptibility to tetany. It is true that there are only eight cases of hyperthyroids in the measured group, but it may be remembered that we had also fourteen cases of hyperthyroidism in our Summer series. A different technique was used in the preparation of the material from these, so that they could not be included in our measured series. There is no doubt, however, as to the activity of the gland. They were the most obvious hyperthyroids of all our series, the condition being such as to attract immediate attention and to form the starting point of this phase of the investigation. They may certainly be added to the eight measured cases of the table, giving a total of twenty-two animals with active thyroid gland, among which there was not a single case of tetany. There is no evidence that hyperthyroidism can be correlated either with the age or the weight of the animals. Rats are less susceptible to tetany at 90 days than at 60 days, as we have already shown, but hyperthyroidism does not occur in a greater proportion of the older than in the younger animals. The material we have from 90-day rats is scanty, and not suitable for measurement, but includes no obviously hyperactive thyroids. The condition appears to be most common, among the 60-day animals, in

the overweight group; but it is not confined to them, as may be seen from the table.

The data obtained from the study of the thyroid in parathyroidectomized rats may be summarized as follows: (a) The average thyroid index of animals which survive the operation is higher than that of those in which fatal tetany occurred. (b) Rats which were hyperthyroid at the time of the operation proved to be immune to tetany.

DISCUSSION

The data presented in the preceding pages are published primarily in the hope that they may be of practical value to those undertaking researches involving parathyroidectomy. During past years we have had a number of requests for information as to the influence of external factors on the susceptibility of rats to tetany, and it seemed worth while to analyse our experience and make it available to others.

From this point of view the situation may be summarized briefly as follows: All series of experiments on factors modifying the response of rats to parathyroidectomy should be carefully controlled in regard to the age and weight of the animals used. For accurate comparisons between experimental and control groups, one should select rats of uniform age and normal weight. If this precaution is taken, there seems to be no reason for confining the series to one season of the year, since seasonal variation appears to be a secondary matter. It is often true that during the Summer an especially large proportion of the members of a colony are sickly; but healthy animals have not, in our series, shown a higher mortality in Summer than in Winter.

Selection of animals on the basis of age and weight is an easy matter; the exclusion of hyperthyroid individuals from a series is, of course, less simple, since it can be done only by examination of the tissues removed at operation. It is, however, an important factor to take into consideration. The accidental inclusion of five hyperthyroid animals in a series of twenty cases would distort the results of any experimental procedure to a serious extent. Hyperthyroidism is the only condition we have yet found which is always accompanied by immunity to tetania parathyreopriva.

It is not the author's intention to venture far into the discussion of the theoretical implications of these data; but a few comments are justified, if only to show that the limitations of what is presented are fully realized.

We have not attempted to determine the cause of parathyroid tetany but have been engaged in a study of the natural sources of immunity to it. These have been held by some to be exogenous, by others endogenous. We are decidedly of the opinion that they are endogenous. Our rats have come from various sources, and have been raised under different conditions of diet, temperature, etc., from time to time. We have not, however, found that any of these differences have affected susceptibility to tetany so long as adequate health was maintained. Under all such conditions which we

have tested, including the feeding and withholding of meat, fifty to sixty per cent of the normal animals survive the operation. Not only is this true throughout the large series, but a similar percentage of survivals is found, on an average, within a group of litter mates. Here, conditions are identical from birth to the time of operation, but our experience indicates that in such homogeneous groups there is still a variation in susceptibility. We must conclude that it rests on some internal differences among the animals.

It appears that advancing age confers a partial immunity to tetany. This is particularly evident in the different response of the animals before and after puberty. There is a marked fall in susceptibility with the establishment of sexual maturity. It is not true, however, that the gonads are directly and exclusively responsible for the change. This was demonstrated by Overholser (1929), who found no difference between the susceptibility of normal and castrated rats, either at 60 or at 90 days of age.

Relaxation of the nervous system, which Hammett considers a very important factor in tetany, may also confer a partial immunity, but does not entirely remove susceptibility. We have been unable, in our work, to trace any variations in the mortality rate to differences in excitability, and do not believe that relaxation is a direct and fundamental cause of survival. The gentling process tends toward a condition of general well-being, and appears to involve other changes than the reduction of muscle tonus.

The theory that susceptibility depends on the condition of the thyroid is a tempting one; but it must be said that our results, so far, give it a moderate support. It may, at this time, be offered only as a working hypothesis, to which there are obvious limitations. In the first place, by the methods employed, we have demonstrated only that a thyroid condition which may be regarded as hyperactive is correlated with 100 per cent immunity to tetany. We have not shown that subnormal thyroids are correlated with tetany. There is a large group of cases in which the thyroids appear normal and in which there is the usual variation in mortality; there are also survivors in the group with subnormal thyroids. It may be that more accurate methods of determining the activity of the thyroid would reveal a closer correlation between the factor and the result of parathyroidectomy; at present we may say only that hyperthyroid animals are immune.

It is also evident that, could one demonstrate such a correlation, the nature of the relation between the thyroid and tetany would not be clear. To show that immunity exists simultaneously with hyperthyroidism does not prove that the two conditions are causally related. The belief that they may be is, indeed, encouraged by the results obtained by Kunde, Oslund, and Kern (1928) on thyroid fed dogs; and similar experiments now in progress in this laboratory indicate a like result.

Finally, we have no information as to the possible mechanism of the thyroid influence supposing it is granted for the sake of argument that ex-

cess of the hormone of this gland prevents tetania parathyreopriva. The thyroid may, of course, influence directly the calcium-metabolism of the body, thus preventing the deficiency of this element in the blood which is believed to be the immediate cause of tetany. On the other hand, it may act through the medium of some other organ, such as the adrenal. Until a thorough study has been made of the conditions of the whole endocrine system after parathyroidectomy, we have but a partial view of the situation. All that we are able to do at present is to record a beginning of such a study in the establishment of the correlation between hyperthyroidism and absence of tetany.

SUMMARY

The report presents an analysis of 244 cases of parathyroidectomy, considering the relations of age, weight, season and thyroid activity to the susceptibility of the white rat to tetania parathyreopriva. The results indicate that the mortality from tetany within 48 hours after parathyroidectomy is about 55 per cent in normal animals 60 days old. The rate is raised in groups of animals which are below normal weight; it is not directly affected by seasonal variations. It decreased to 13 per cent in a small series of animals parathyroidectomized at 90 days of age. No connection could be traced between susceptibility and nervous condition.

In a series of 45 animals the condition of the thyroid at the time of operation was determined by weighed paper reconstructions. It was found that animals which died of tetany had, on the average, less active thyroids than those which survived. It was also observed that when the measurement of thyroid activity was above the standard deviation for the series the rats were, without exception, immune to the immediate effects of parathyroidectomy.

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THE PREPARATION OF ADRENAL CORTICAL HORMONE [1, 2]

J. J. PFIFFNER AND W. W. SWINGLE
From the Biological Laboratory
PRINCETON UNIVERSITY

The preparation of a physiologically potent extract of the adrenal cortex, suitable for intravenous administration in laboratory and clinical experimentation, was placed upon a firm footing in 1929 (1) when conclusive evidence was presented by the authors to show that the cortical hormone, essential to the maintenance of life, can be readily extracted from beef adrenal glands with lipid solvents. It was also observed at that time that the solubility of adrenalin in the common lipid solvents was markedly influenced by the presence of lipid materials, particularly phospholipid. Consequently the crude lipid fractions which contained the cortical hormone also contained variable amounts of adrenalin. In order to obtain a relatively pure preparation of cortical hormone it was necessary therefore to fractionate with two objectives in view: (1) the separation of the cortical hormone from lipid material, and (2) the separation from adrenalin.

A flow sheet by means of which both these objectives have been attained is presented in Figure 1. Highly potent extracts suitable for intravenous injection either in man or animals can be readily prepared by this fractionation procedure (2-9). This method has never failed to yield a highly potent product in about two hundred lots of material which have been worked up in this laboratory.

The object of the permutit filtration (Figure 1) is to reduce the adrenalin concentration to a level (about 1 part in 2 million when 1 cc. of extract represents 30 gm. of fresh beef adrenal cortex) at which the material can be used intravenously in relatively large doses without obtaining an adrenalin effect. Another fractionation step by means of which this objective can be accomplished is by washing a solution of an active fraction in a non-miscible solvent such as benzene or ether with 0.1 normal sodium hydroxide (6). The cortical hormone is found in the non-miscible solvent phase. Highly potent extracts containing less than one part of adrenalin in 4,000,000 can be readily prepared by this procedure (10).

In the earlier fractionation studies the criterion of activity used was the survival of bilaterally adrenalectomized cats. The life-span of untreated bilaterally adrenalectomized cats has been established in this laboratory as 9.8 days in a series of 75 animals. With the type of extract prepared according to the flow sheet outlined in Figure 1, bilaterally

1. Read before the Fifteenth Annual Meeting of the Association for the Study of Internal Secretions, Philadelphia, June 9, 1931.
2. This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

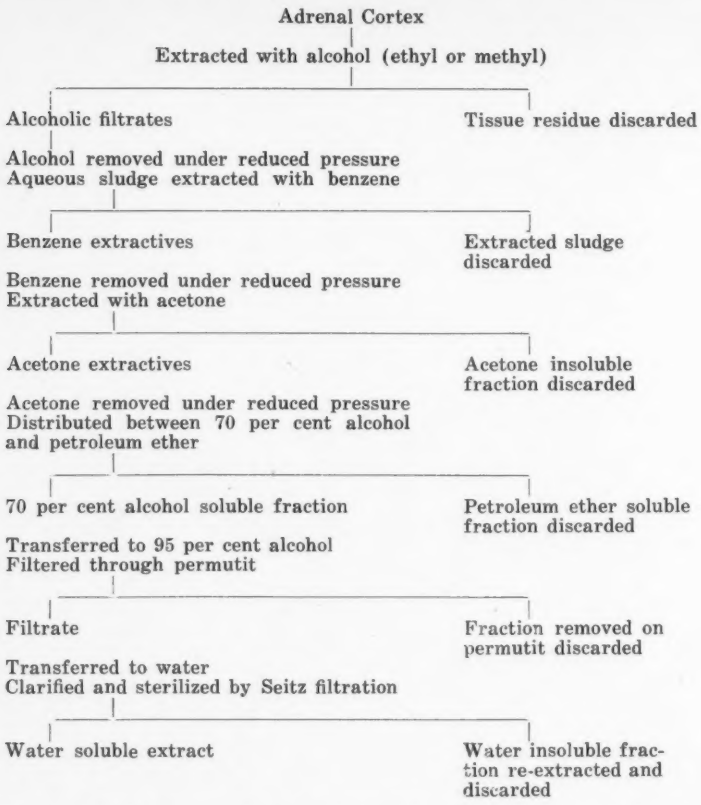
Adrenal Cortex
Extracted with alcohol (ethyl or methyl)
Alcoholic filtrates
Tissue residue discarded
Alcohol removed under reduced pressure
Aqueous sludge extracted with benzene
Benzene extractives
Extracted sludge discarded
Benzene removed under reduced pressure
Extracted with acetone
Acetone extractives
Acetone insoluble fraction discarded
Acetone removed under reduced pressure
Distributed between 70 per cent alcohol and petroleum ether
70 per cent alcohol soluble fraction
Petroleum ether soluble fraction discarded
Transferred to 95 per cent alcohol
Filtered through permutit
Filtrate
Fraction removed on permutit discarded
Transferred to water
Clarified and sterilized by Seitz filtration
Water soluble extract
Water insoluble fraction re-extracted and discarded

Fig. 1. Method of fractionation for the preparation of adrenal cortical hormone.

adrenalectomized cats can be kept in apparently normal health for as long as the extract treatment is continued. The weight charts of two typical cases are given in Figures 2 and 3.

Adrenalectomized animals can not only be kept alive and in good physical condition by injections of cortical hormone but they can also be brought back to normal condition from the severe prostration of adrenal insufficiency. In Figures 5 and 6 are given the weight changes of 2 bilaterally adrenalectomized animals that were allowed to pass into the complete prostration of adrenal insufficiency following the removal of the second adrenal gland before treatment with the cortical hormone was instituted. We have many cases in our records of animals which in the course of testing different fractions for activity, were allowed to pass into severe insufficiency six to ten times in the course of a few months.

A striking symptom seen in the cat suffering from adrenal insufficiency is a marked drop in the rectal temperature. There is also a marked

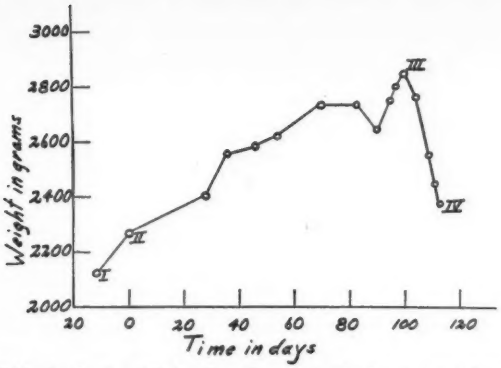

Fig. 2. Weight chart of a bilaterally adrenalectomized cat treated with cortical hormone. I, R. adrenal removed; II, L. adrenal removed, treatment started 24 hours later; III, treatment discontinued; IV, death from adrenal insufficiency.

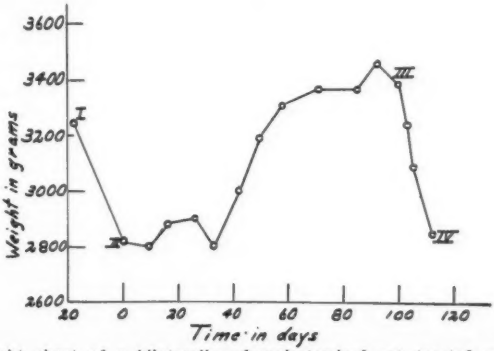

Fig. 3. Weight chart of a bilaterally adrenalectomized cat treated with cortical hormone. I, R. adrenal removed; II, L. adrenal removed, treatment started 24 hours later; III, treatment discontinued; IV, death from adrenal insufficiency.

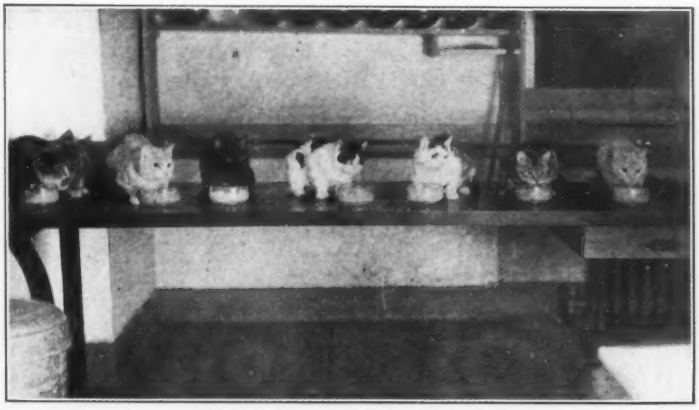

Fig. 4. A series of seven bilaterally adrenalectomized cats treated with cortical hormone. The picture was taken by flashlight 100 days after the removal of the adrenal glands. All seven animals died with typical symptoms of adrenal insufficiency within three weeks after withdrawal of treatment.

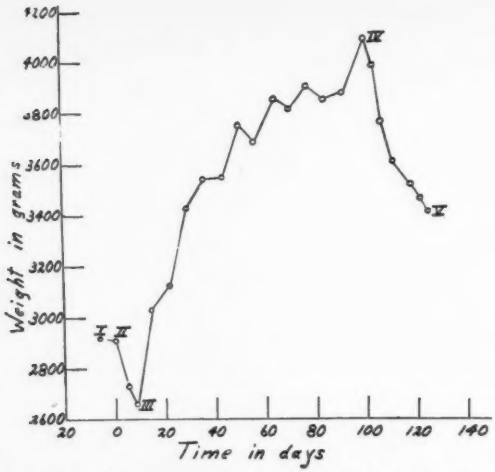

Fig. 5. Weight chart of bilaterally adrenalectomized cat treated with cortical hormone, following the exhibition of severe symptoms of adrenal insufficiency. I, R. adrenal removed; II, L. adrenal removed; III, animal prostrate, treatment begun; IV, treatment discontinued; V, death from adrenal insufficiency.

drop in the metabolic rate (11). In Figure 7 are presented the rectal temperature readings of an animal that was allowed to develop very severe symptoms and then returned to a normal condition with the hormone. Coincident with the return of the rectal temperature to normal there is the development of a ravenous appetite, a return to the normal level of metabolism and a disappearance of muscular asthenia. The animal usually recovers its normal appetite before the rectal temperature and heat production has reached a normal level and before the asthenia has disappeared. With subcutaneous injections, it requires from 24 to 72 hours for a complete recovery from severe prostration.

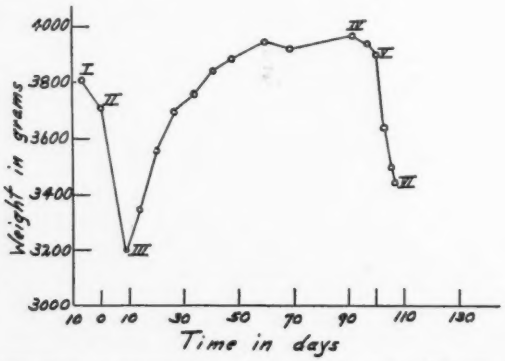

Fig. 6. Weight chart of bilaterally adrenalectomized cat treated with cortical hormone, following the exhibition of severe symptoms of adrenal insufficiency. I, R. adrenal removed; II, L. adrenal removed; III, animal prostrate; treatment begun; IV, dosage reduced to ¼ cc. per kilogram daily; V, treatment discontinued; VI, death from adrenal insufficiency.

The results obtained with the cortical hormone on bilaterally adrenalectomized cats as regards maintenance of life and relief of severe adrenal insufficiency symptoms have been duplicated on bilaterally adrenalectomized dogs (12). The cortical hormone has also been exhibited successfully in the crises of Addison's disease (8, 9).

We have been unable to detect any toxic reactions or overdosage phenomena in the administration of huge doses of cortical hormone to cats and dogs.

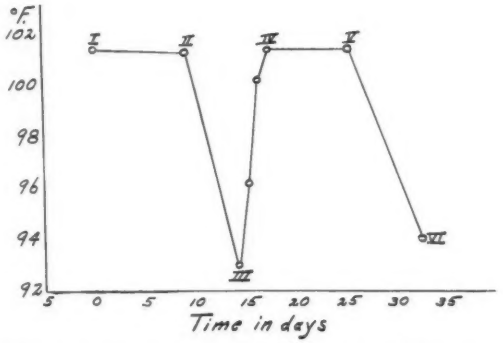

Fig. 7. Rectal temperature chart of a bilaterally adrenalectomized cat treated intraperitoneally with cortical hormone. I, second gland removed; II. no symptoms; III. prostrate; treatment begun; IV, no symptoms; V, treatment discontinued; VI, prostrate (died of adrenal insufficiency).

SUMMARY

The fractionation procedure outlined yields a preparation of adrenal cortical hormone suitable for subcutaneous or intravenous administration in animals and man.

Bilaterally adrenalectomized cats and dogs can be kept alive and in normal health indefinitely with adequate daily injections of the hormone. They can be brought back to normal health and activity from the complete prostration of adrenal insufficiency.

The cortical hormone has been used successfully in the crises of Addison's disease.

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Abstract Department

Role of adrenalin in the regulation of carbohydrates and fats in the blood (Vegetativ-endokrines System als Regulator des intermediären Stoffwechsels. I. Mitteilung: Die Rolle des Adrenalins bei der Regulation der Kohlehydrat- und Fettbestandteile des Blutes). Alpern, D. and L. Tutkewitsch, Biochem. Ztschr. **215**: 319. 1929.

Twenty-two dogs received injections of suprarenin, blood being taken before the injection and 5, 20 and 60 minutes after. Blood was analysed for sugar, lactic acid, fat, cholesterol, ketone substances, and in some cases total and residual nitrogen. The dogs were 20 hours fasting in all experiments, and in some cases were given phlorrhizin, or thyroxin and peptone, to free the blood stream of carbohydrate. Experiments were also carried out with previous administration of oleic acid, and of colloidal dyes (Trypan blue, Congo red) and crystalloidal dyes (Rhodamine, Cyanol). From their analytical results (which are given in detail) the authors conclude that the hyperglycemia with lowered blood fat observed in normal fasting dogs after adrenalin administration is not the result of chemical transformation of fat into sugar, but results from the change of the state of the liver glycogen by the penetration of colloidal material into that organ. Emulsified fat is effective, also colloidal dyestuffs. Crystalline dyestuffs are not.—B. S. Walker.

The combination of iron salts with prepared adrenal extracts in the treatment of cancer in white mice (Association d'un sel de fer aux extraits de capsules surrénales préparées dans le traitement du cancer expérimental de la Souris). Arloing, F., A. Josserand and J. Charachon, Compt. rend. Soc. de biol. **103**: 1116. 1930.

Adrenal extract from rabbits, which have been injected with extracts of mouse cancer, have the power of arresting the growth of epithelioma in mice. The addition of iron sodium citrate does not increase the potency of the original extract.—J. C. D.

The synthesis of glutathione in the adrenal gland (Synthèse du glutathion dans la glande surrénale). Binet, L., A. Blanchetière and A. Arnaudet, Compt. rend. Soc. de biol. **104**: 56. 1930.

Twelve adrenal glands (animal not stated) were perfused with citrated blood to which cystine and glutamic acid had been added. There was an increase of glutathion in the gland and in the blood flowing from the gland. —J. C. D.

Attempted autotransplantation of the adrenal cortex. Johnson, Adelaide and V. Johnson, Am. J. Physiol. **97**: 392. 1931.

Attempts to autotransplant the adrenal cortex of 46 dogs to the thyroid, omentum, testis, kidney and liver were uniformly unsuccessful.—R. G. H.

The protection of the function of the adrenals by diphtheria antitoxin (Sur la protection des fonctions surrénaliennes par l'anatoxine diphtérique). Mouriquand, G., A. Leulier and P. Sédallian, Compt. rend. Soc. de biol. **104**: 22. 1930.

If the guinea pigs are given antitoxin and two months later receive a lethal dose of diphtheria toxin, the usual complete disappearance of adrenin from the medulla of the gland does not occur. Instead, the adrenin content remains unchanged.—J. C. D.

The local damage caused by adrenin as favorable to the development of bacterial infection (Role favorisant des perturbations locales causées par l'adrénaline sur le développement des infections microbiennes). Renaud, M. and A. Miget, Compt. rend. Soc. de biol. **103**: 1052. 1930.

The local scar at the site of injection is very vulnerable to bacterial invasion, as proved by injecting organisms of various grades of pathogenicity into the scar immediately after the adrenin.—J. C. D.

Adrenalin and the metabolism of exercise. Ring, G. C., Am. J. Physiol. **97**: 375. 1931.

A treadmill for rats was devised and the metabolism of rats during activity determined. Small doses of adrenalin (0.001-0.002 mgm. per 100 grams) given to fatigued rats lowered their respiratory metabolism in exercise. In man, as in the rat, physiological amounts of adrenalin (0.5 mgm. per person) given after fatigue caused a lowering of the respiratory metabolism of exercise. Without previous fatigue, the metabolism of exercise was increased by a similar amount of adrenalin. The respiratory quotients of exercise were found to be lowered by adrenalin. The results which are reported in this paper are consistent with the inference that if adrenalin is given late in a fatiguing exercise, the body usually goes on to a larger fat metabolism.—R. G. H.

Diagnosis and treatment of Addison's disease. Rogoff, J. M., Canad. M. A. J. **24**: 43. 1931.

A general resumé of the subject, with some account of good results following use of "interrenalin."—A. T. C.

Comparative study of the testes and ovary of immature rats injected with urine from a woman in early pregnancy (Etude comparée du testicule et de l'ovaire du rat impubère traité par l'urine de femme gravide des quatre premiers mois).

Histological changes in the genital tract of the immature male rat injected with urine from a woman in early pregnancy (Les modifications histologiques du tractus génital du rat male impubère traité par l'urine de femme enceinte des quatre premiers mois). Bourg, R., Compt. rend. Soc. de biol. Paris, **104**: 107; 109. 1930.

The testes show enlargement and proliferation of the interstitial cells while the seminiferous tubules are not much affected. The entire genital tract and accessory glands show hypertrophy. These results resemble those produced by implanting the anterior lobe of the hypophysis.—J. C. D.

The latent period for the appearance of secondary sex characters in capons treated with bulls' serum. Persistance of psycho sexual reactions after cessation of treatment (Le temps de latence des caractères sexuels secondaires chez le chapon traité par le sérum de taureau; persistance du comportement psycho-sexuel aprés cessation du traitement). Busquet, H., Compt. rend. Soc. de biol. **103**: 1238. 1930.

Caponized chickens were fed young bull serum by mouth. If caponization was done at one month and treatment begun at once, male sex characters developed at 7 months, that is a month later than in normal controls. In adult animals operated on at 9 to 15 months, treatment for 2 months restored the secondary characters. If the operation was incomplete, the restoration was more rapid. Castrated cocks lose their secondary sex characters at once. In capons, which have received bull serum over a period of 8 months, cessation of treatment results in loss of the comb only. If these birds are now subjected to an operation simulating castration, the other secondary characters disappear. The rapid loss of secondary sex characters in the cock following castration is due to operative shock rather than the actual gonadectomy. —J. C. D.

Notes on the clinical use of certain placental extracts. Campbell, A. D. and J. B. Collip, Canad. M. J. **23**: 633. 1930.

Collip has prepared from the human placenta an extract, emmenin, that is effective when given by mouth. In a clinical study of 135 cases it was found that emmenin does not alter normal menstrual cycles. Its effect in dysmenorrhoea has been particularly encouraging. It appears to correct certain types of amenorrhoea of recent origin. It definitely lengthens the cycles in polymenorrhoea. It relieves menopausal symptoms of recent origin, but does not relieve symptoms in castrates. An anterior-pituitary-like principle from the placenta arrests certain forms of metrorrhagia. Emmenin was found to have no effect on the male.—R. G. H.

Placental hormones. Collip, J. B., Canad. M. A. J. **23**: 631. 1930.

From study of the literature and from his own results Collip concluded that the human placenta contains at least three distinct active principles, all producing oestrus in the immature female rat, oestrin, emmenin (soluble in 85% alcohol) and a third prepared from the alcohol-insoluble material, and resembling that of the anterior pituitary. Emmenin is very similar to oestrin in its ultimate physiological effects, but is ineffective in the castrate, whence it may be concluded that it functions directly or indirectly by stimulation of the intact ovary. The third fraction differs from emmenin in being ineffective orally, by producing corpora lutea in the immature rat coincident with induced oestrus, and by causing an increase in the rate of growth of the accessory sex glands in the immature male rat.—A. T. C.

Cause of "painful breasts" and treatment by means of ovarian residue. Cutler, M., J. A. M. A. **96**: 1201. 1931. Abst., A. M. A.

The author states that clinical, pathologic and experimental evidence clearly indicates that excessive epithelial and connective tissue hyperplasia giving rise to diffuse generalized pain and nodularity in the breasts in relation to menstruation may be due to excessive corpus luteum stimulation. In patients suffering from "painful breasts" the corpus luteum dominates the ovarian metabolism and by inducing an excessive epithelial and connective tissue hyperplasia causes diffuse pain and generalized nodularity of the breasts. At the same time the overactive corpus luteum suppresses ovulation and exerts an estrus-inhibiting influence leading to a hypofunction of the follicular and interstitial elements of the ovary, as indicated by the short and scanty menstrual periods in these cases. The administration of ovarian residue apparently tends to cause a cessation of abnormal epithelial and connective tissue hyperplasia by counteracting the excessive corpus luteum secretion, thereby diminishing or removing its overstimulating influence on the breast elements. The administration of ovarian residue by mouth has resulted in relief of pain and tenderness in a number of patients suffering from this condition. A definite softening of the breasts and actual disappearance of painful nodules have been observed in some cases. The menstrual periods in many are restored to a more normal state and the general state of the patients is improved.

The gonad stimulating and the luteinizing hormones of the anterior lobe of the hypophysis. Fevold, H. L., F. L. Hisaw and S. L. Leonard, Am. J. Physiol. **97**: 291. 1931.

The anterior lobe of the hypophysis secretes 2 hormones which act on the ovary, a gonad stimulating factor which stimulates follicular growth and a luteinizing factor which causes lutein growth. These 2 hormones have been extracted quantitatively from dried anterior lobe tissue by means of aqueous pyridine. The 2 hormones have been separated from one another into 2 different preparations each of which gives a different physiological reaction. When the 2 fractions are again united the resulting preparation is entirely similar to the first crude extract. The luteinizing hormone cannot act on the immature ovary. The infantile ovary must be stimulated to follicular activity by the gonad stimulating hormone before a characteristic "mulberry" ovary can be produced.—Authors' Summary.

The oestral cycle in the uterus (Experimentelle Untersuchungen über die Beziehungen der Uterusfunktion zu den zyklishchen Vörgangen an den Ovarien). Kok, F. and H. Seel, Arch. f. exper. Path. u. Pharmakol. **145**: 1. 1929. Abst., Physiol. Absts. **16**: 132.

Uteri were removed from mature non-pregnant pigs at different periods of the oestral cycle and suspended in salt solution so that their movements were recorded. A regular oestral cycle in the behaviour of the uterus was thus detected. The spontaneous activity reaches a maximum at the time of the bursting of the follicles. Adrenalin produces prolonged contraction of uteri removed between the bursting of the follicles and the end of the corpus luteum stage, but during the rest of the cycle its chief effect is relaxation, though this is often preceded by a brief contraction.

Friedman's hormone test for pregnancy. Magath, T. B. and L. M. Randall, J. A. M. A. **96**: 1933. 1931. Abst., A. M. A.

The authors believe that although the hormone pregnancy test devised by Friedman, using urine which is injected intravenously into rabbits, is simple to perform, certain precautions are necessary. In the first place, the first urine passed in the morning should be used and should be injected within an hour, or the specimen should be kept on ice until it is used. Urine older than five hours probably should not be used. If the urine is cloudly it should be filtered. Rabbits younger than two and a half months should not be used, and there is no objection to using old animals if they have not recently copulated. It is absolutely essential that rabbits be kept under such conditions as to insure their not being pregnant as well as not having recently copulated. If the rabbits are young, care will have to be exercised to be sure that females and not males are selected for the test, for the external genitalia are not so clearly recognized as in older animals. It is best to isolate animals in single cages for three weeks before using them, thus avoiding any of these difficulties. Sterile technic is not necessary, and from 7 to 15 cc. of urine should be injected slowly into the marginal ear vein of the rabbit. Thirty hours should elapse before the animals are examined, else the test may be indefinite. Positive tests are indicated by the presence of corpora lutea and corpora hemorrhagica, which are detected by gross inspection. If they are not clearly evident, the test had best be considered negative. In the authors' series of positive animals, marked injection of the uterus and oviducts was striking. The test is both practical and accurate. It is of great value in distinguishing either early or late pregnancy from other conditions. Perhaps its greatest value will be in detecting early pregnancy in cases in which continuation of the pregnant state would be dangerous to the physical well being of the patient.

On oestrus-producing product of the male sex glands (Sulla presenza di una sostanza estrigena nell ghiandola sessuale maschile). Maino, M. and B. Frattini, Boll. d. Soc. ital. di biol. sper. **5**: 1065. 1930. Abst., Physiol. Absts. **16**: 129.

A crystalline substance was obtained by extraction of testes with water and repeated precipitation with salts of heavy metals. This substance was injected into castrated male rats and found to cause activity of the cells of the seminal vesicles. When injected into castrated females it caused typical oestrus. Conversely, when follicular extract was injected into castrated males the cells of the vesiculae seminales were stimulated to activity. It is concluded that the two hormones must be similar.

Hormone exchange between parabiotic animals. Hormones of the anterior lobe of the hypophysis and the testicle (Exchange hormoniques chez les animaux en parabiose. Hormones du lobe antérieur de l'hypophyse et du testicule). Martins, T., Compt. rend. Soc. de biol. **103**: 1341. 1930.

In parabiotic rats and mice where one animal is a castrated male and the other a normal male, there is an increase in size of the seminal vesicles and prostate in the normal but atrophy in the castrated. Even if the vesicles and most of the prostate are removed from the normal rat, there is atrophy in the other. In mice, if one animal is a cryptorchid and the other a castrate, there is atrophy in the latter and little change in the former. Evidently the anterior lobe hormone passes from castrate to normal in sufficient quantities to cause enlargement of the vesicles and prostate, but the testicular hormone is not present in large enough amounts to prevent atrophy of these organs in the castrate member of the pair.—J. C. D.

Cysts of graafian follicle and corpus luteum. Miller, H. P., J. A. M. A. **96**: 1569. 1931. Abst., A. M. A.

The author reports 4 cases of hemorrhage from a follicular cyst or a cyst of the corpus luteum. One case was a typical example of a massive intra-abdominal hemorrhage closely resembling a ruptured tubal pregnancy even to the pain in the neck and shoulder. Three cases were of the moderate type and the form that is especially liable to be mistaken for something else. The

treatment in all the cases consisted of resection of the cyst and closing the area with lock sutures of number 2 plain catgut. The author believes that these cases call for immediate operation because one has no way of knowing the extent to which bleeding may go. Undoubtedly, many small hemorrhages are overlooked. When the condition is thought of in differential diagnosis, the picture is fairly clear cut; when doubt exists, a diagnostic vaginal puncture should be made.

Four cases of eunuchoidism (Vier Fälle von Eunuchoidismus). Minakuchi, H., Folia Endocrinologica Japonica, **6**: 103. 1931.

The author investigated 4 eunuchoids. In every case hypoplasia of the gonads was present with an absence of sex desire; 1 patient also had epileptic attacks. On the basis of the clinical symptoms, faulty development of the sex organs and secondary sex characteristics, the characteristic fat depositions, and the abnormal lengths of the extremities, eunuchoidism was diagnosed. The x-ray picture in 2 cases showed open epiphyses of the bones and a somewhat diminished heart, and in 1 case the duct of Botalli remained open. The blood picture showed a lessening of the neutrophile polynuclear leucocytes and an increase of the lymphocytes. All cases were weakly sensitive to adrenalin and strongly sensitive to pilocarpine and atropin in the pharmacodynamic tests. From the different functional tests of the vegetative nervous system it was shown that all 4 cases were vagotonic. The sugar tolerance lay within the normal limits although approaching the upper limit in most cases. Protein metabolism showed no appreciable deviation from the normal. The basal metabolism in all cases lay almost within the normal range but with a definite inclination to a decreased metabolism. The specific dynamic action of protein in 3 cases occurred at the lower boundary of the normal values.—J. Gagnon.

Modification of Aschheim-Zondek test for pregnancy. Reinhart, H. L. and E. Scott, J. A. M. A. **96**: 1565. 1931. Abst., A. M. A.

In their modification of the Aschheim-Zondek test, the authors use female rabbits in the place of white mice as the test animal. It is necessary to know that the doe is over three months old and is not pregnant, but otherwise the history of the rabbit is unimportant. The particular advantage in using the rabbit is the fact that the female does not ovulate without copulation. If the ovary of the adult nonpregnant doe is carefully examined at any time, there will be seen several large vesicles which are ripe graafian follicles. It is advisable to become familiar with these before endeavoring to read the end-results of a test, because they have been misinterpreted by those who were unfamiliar with the normal ovary of the rabbit. These ripe graafian follicles rupture with escape of the ova about the time of copulation. The ruptured graafian follicle is then converted into a corpus hemorrhagicum, which in turn is converted into a corpus luteum of pregnancy. This series of events occurs normally only following copulation. Ovulation therefore is not cyclic but periodic, and corpora hemorrhagica and corpora lutea are normally present only during pregnancy. It is this peculiarity in the normal ovarian physiology that makes the rabbit the test animal of choice in this modification of the Aschheim-Zondek test, because the test is essentially founded on the principle that ovulation and the formation of corpora hemorrhagica do not occur in the nonpregnant doe and, when found, are indicative of having been induced by the hormone of the anterior pituitary body, which hormone is excreted in large amounts in the urine of the pregnant woman. The authors give a detailed description of the technic of the test. Their experience with this modification of the Aschheim-Zondek test consists of a series of 150 clinical cases. The results in each case have been carefully checked by the subsequent clinical course of the patient whose urine was examined. In this series they found 82 cases with a negative, and 68 cases showing a positive reaction. In 2 cases only was the diagnosis not substantiated by the subsequent clinical course. Although the series of cases reported is inadequate for definite conclusions, the authors feel that the results obtained are of sufficient importance to warrant extensive trial, and that the simplicity of the technic will facilitate the utilization of the test in laboratories and clinics where the Aschheim-Zondek test has not hitherto been available. The availability of the adult doe as a test animal, without particular reference to its age and the rapidity with which the end-results may be obtained, are points that also deserve emphasis.

The effect of ovarian grafts from new-born dogs upon old dogs (L'action des greffes d'ovaires de chiennes nouveau-nées chez les chiennes âgrées). Truffi, G., Boll. d. Soc. ital. di biol. sper. **3**: 430. 1928. Abst., Rev. franç. de gynec. et d'obst. **26**: 127.

The author made ovarian grafts from young dogs (5-10 days old) into the subcutaneous tissue of the abdomen of old dogs (16-19 years). The graft was changed quickly into a mass of connective tissue. At the same time phenomena, which were distinctly rejuvenescent, appeared in the genital apparatus of the grafted animal, becoming suddenly manifest at the end of 15-20 days. The ovary assumed an embryonic aspect, with the formation of new Pflüger's tubes, but without any ovules. These phenomena of regeneration were also produced in the stroma, where numerous interstitial elements arose. As for the uterus, microscopically it assumed the appearance of the organ in its active phase; histologically there was an active process likewise in the mucosa, stroma, and muscular tissue. The author was able to make comparative studies of pieces of the ovary and of the uterus, removed by laparotomy from the same animals before the graft.—J. Gagnon.

Menstruation and irregular uterine hemorrhage of ovarian origin. Young, J., Brit. M. J. **2**: 1031. 1930.

Approximately the first half of the article is concerned with a discussion of the rapidly changing modern views of the physiology of the sex cycle. The later half of the paper is concerned with abnormal uterine hemorrhage of ovarian origin. The early work of Cushing is cited, showing the failure of sexual development in certain pituitary disorders. Evans and others have shown that the ovaries of immature animals become activated by the injection of extracts of the anterior lobe of the pituitary. The view most generally held until recently that menstruation is controlled by the follicle-corpus luteum apparatus in the sense that it occurs when the corpus luteum begins to retrogress has been finally invalidated by Corner, Hartman, and Van Herverden. These investigators show that in monkeys menstruation can occur regularly when there is no follicle-corpus luteum cycle taking place in the ovaries. There is evidence that a similar phenomenon can occur in women. The exact mechanism of the regulation of the sex cycle is still a matter of speculation but it has been more commonly believed that the cycle is controlled by variations in ovarian hormones under the pituitary influence. Pathological uterine hemorrhage is discussed from the standpoint of the tripartite mechanism: (1) pituitary; (2) ovary; (3) uterus. The author admits that the data on pathological uterine hemorrhage with reference to the pituitary are few but suggests that the possibility of the well known influence of shock or excitement on menstruation may be through the pituitary. There are pathological and clinical data to show that in many cases of uterine bleeding, formerly defined by such loose pathological terms as fibrosis uteri, metritis, and glandular endometritis, the real cause lies in ovarian dysfunction. To support this view the author cites Shaw's recent clinical and pathological studies on 200 cases of uterine bleeding. The foregoing statements indicate that many cases, which were formerly classified as bleeding of uterine origin under various vague pathological terms, should be now regarded as ovarian in origin. The author emphasizes the necessity of diagnostic curettage in cases of excessive bleeding in women over 40. Having excluded malignancy, he prefers treatment by x-radiation if the bleeding recurs after curettement. Radium may be used as an alternative. In younger women the author suggests curettage, general hygienic measures, calcium salts, sistomensin, and agomensin.—R. W. Te Linde.

Hormones of urine during pregnancy (Hormonal Schwangerschaftsreaktion aus dem Harn bei Mensch und Tier). Zondek, B., Klin. Wchnschr. **9**: 2285. 1930. Abst., Physiol. Absts. **16**: 131.

In horse's urine during pregnancy a large amount of folliculin and a small amount of the follicle-ripening hormone of the pituitary anterior lobe are present. The pituitary hormone responsible for luteinization is absent. It is calculated that a mare's urine during the period of gestation would yield 250 million mouse units of folliculin. The folliculin cannot be extracted from the urine with ether, but is completely removed by charcoal.

The pituitary gland in the ascidians (Molgula manhattensis). Butcher, E. O., J. Exper. Zool. **57**: 1. 1930.

An effort was made to determine the character of the neural gland in the ascidians, since it had been referred to by various authors as either a lymph gland, kidney, salivary gland, or pituitary. A careful study of sections of the gland of Molgula manhattensis showed that the cells of the gland did not resemble blood cells. Injections of indigo carmine, phenol red, and trypan blue into the pericardial cavity, into the blood stream, and into the gland furnished no evidence that the gland was excretory in nature. Extracts of the gland were found to contain no digestive enzymes, and, therefore, it evidently did not function as a salivary gland. Fifty glands were desiccated in C. P. acetone and were sent to Dr. Oliver Kamm who made an extract in acetic acid in accordance with the usual method of extracting the active substance of the posterior pituitary except that 0.1% acid was used and a 1:1000 solution prepared. Testing the solution, he found that it contained 0.4 unit of oxytocic activity per cubic centimeter. The neural gland material, therefore, had about 20% of the strength of the U. S. standard powder. In comparison to the pituitary glands of cattle, these glands are probably as potent, since the acetone-desiccated material obtained from whole glands of cattle is expected to test only 10 to 20% of the U. S. standard powder. No data were obtained concerning the blood-pressure principle. These determinations provide evidence that the neural gland of the ascidians is a pituitary. This would seem to be the most primitive pituitary gland thus far discovered in the animal kingdom.—Author's Abst.

Occurrence of female sex hormone and anterior pituitary hormone in the blood and urine of the newborn (Das Vorkommen von weiblichem Sexualhormon und Hypophysenvorderlappenhormon im Blute und Urin von Neugeborenen). Brühl, R., Klin. Wchnschr. 8: 1766. 1929.

Female sex hormone was found, irrespective of sex, up to the fourth day in the urine, also in cord blood and amniotic fluid. It was not found in milk or colostrum except in isolated cases. Anterior pituitary hormone (Reaction I of Aschheim and Zondek) was found in the urine only in half the cases, and only up to the second day; the difference was not according to sex. It was found in small amount in cord blood, not in amniotic fluid at full term or in milk (one exception). By animal experimentation it was shown that milk secretion could be induced by a period of treatment with female sex hormone (100 mouse units per day for 18 days with infantile male guinea pigs), the appearance of secretion being dependent upon cessation of the hormone treatment. During the period of administration there was increase in size of the mammary glands. Hence the secretion of witches' milk may be associated with the disappearance of the hormone from the child's circulation.—B. S. Walker.

Histological changes in the hypophysis of animals suffering from flourine cachexia (Modifications histologiques de la glande hypophysaire dans la cachexie fluorique). Cristiani, H., Compt. rend. Soc. de biol. **103**: 981. 1930.

General atrophy of the cells is the histological picture seen in the pituitaries of guinea pigs dying under these conditions.—J. C. D.

Anterior pituitary hormone and male sexual organs (L'hormone du lobe antérieur de l'hypophyse et les organes génitaux mâles). de Jongh, S. E., Arch. neerl. de physiol. **15**: 470. 1930. Abst., Physiol. Absts. **16**: 128.

Material obtained from pregnancy urine injected into young mice or rats for 15 days produces a marked increase in the growth of the secondary sex organs provided normal or unilaterally castrated animals are employed. The injections have no effect on castrates. Hence the anterior pituitary hormone from urine stimulates the testis; examination of that organ shows that the effect is upon Leydig's cells; no change in spermatogenesis was observed even with large doses.

Studies of phosphate and chloride excretion in cases of Fröhlich syndrome. Ling, S. M., S. T. T. Woo and H. C. Chang, Nat. M. J., China, **16**: 545. 1930.

In 2 cases of Fröhlich syndrome, phosphate excretion appeared to be normal. On administration of pituitrin, both urinary phosphate and chloride increased in concentration as the volume of urine was reduced.

—Authors' Summary.

Effect on the blood sugar and inorganic phosphorous of the hypertensive hormone (pitressin) and the ocytocic principle (pitocin) of the posterior lobe of the hypophysis (Action des principes hypertenseur (Pitressin) et ocytocique (Pitocin) posthypophysaires sur la glycémie et le phosphore anorganique du sang). Nitzescu, I. I. and G. Benetato, Compt. rend. Soc. de biol. **103:** 1359. 1930.

Dogs and rabbits were given these preparations by various routes. Intravenous injection was most effective. Pitressin gave a marked hyperglycemia and an increase of phosphorus. Pitocin produced hyperglycemia to a slight degree and did not affect the phosphorus.—J. C. D.

The effect of anterior lobe pituitary extract on egg laying (Über die Wirkung der Extrakt des Hypophysenvorderlappens und aus Schwangerharn auf die Ovulation des Huhns). Noether, P., Arch. f. exper. Path. u. Pharmakol. **150:** 326. 1930. Abst., Physiol. Absts. **16:** 131.

The previous statement that anterior lobe pituitary extract stops hens from laying eggs is confirmed in very clear experiments. The extract used was a simple saline extract which lost its activity on storage. A freshly prepared extract was dried in vacuo, and the residue was found to retain its activity on keeping below 0°C. The acetone-dried powder of Loeser possessed the action in quantities like 30 mgm. (=180 mgm. fresh gland).

Antidiuretic action of pituitrin (Über die Wirkung des Pituitrins auf die Wasserausscheidung durch die Niere). Poullson, L. T., Ztschr. f. d. ges. exper. Med. **71:** 577. 1930. Abst., Physiol. Absts. **16:** 43.

Experiments on healthy young adults showed that pituitrin alone had no effect on the concentration of the blood. After administration of water pituitrin caused a rapid diminution of the diuresis and considerable hydraemia. The antidiuretic action was analysed by estimation of the creatinine and sulphate of blood and urine, and of the excretion of urea. It is concluded that pituitrin affects not glomerular filtration, but the absorptive power of the tubules, and that this increased absorption takes place in the proximal part of the tubule. The possibility of dilution diuresis playing a very great part in physiological conditions is doubted.

The action of the extracts of posterior lobe of hypophysis (pitocin and pitressin) on the calcium and phosphorous of the blood (Action de l'extrait du lobe postérieur de l'hypophyse (Pitocine et Pitressine) sur le calcium et le phosphore du sang). Urechia, C. I., I. Grose and Retezeanu, Compt. rend. Soc. de biol. **103:** 1363. 1930.

In 14 patients suffering from mental illness, the hypertensive extract, pitressin, when given by vein reduced the blood calcium slightly and did not affect the phosphorous. Pitocin, the ocytocic substance, did not affect the calcium but slightly increased the blood phosphorous in 7 cases.—J. C. D.

Anterior lobe of hypophysis: its hormones in relation to placenta. Zondek, B., Zentralbl. f. Gynäk. **55:** 1. 1931. Abst., J. A. M. A. **96:** 1274.

By means of the implantation test, Zondek could demonstrate that the hormone content of the anterior lobe of the hypophysis is quantitatively about the same in man as in woman. Since during pregnancy there is an excessive production of the hormones of the anterior lobe of the hypophysis, the question arises whether the hormones are produced only in the hypophysis or whether they are produced partly in the placenta. To answer this question the author made tests on human beings and on horses, cows and hogs. The hormonal conditions in regard to the hormones of the anterior lobe of the hypophysis were found to be as follows: 1. In pregnant women the blood as well as the urine contains excessive amounts of the hormone of the ripening of the follicles, as well as of the hormone effecting luteinization. In cows and hogs there is no increased hormone production during pregnancy. Neither blood nor urine shows an increased hormone content. 2. The human placenta contains hormones, however, only in comparatively small quantities, from 2 to 3% of the quantities found in the blood and urine. The placentas of cows and of hogs do not contain hormones. 3. The anterior lobe of the hypophysis

of the pregnant woman contains either no hormones at all or extremely small quantities. In the anterior lobe of the hypophysis of pregnant cows and hogs there are the same quantities of hormones as in nonpregnant animals. In the pregnant horse there is likewise an overproduction of the hormones. But whereas in the pregnant woman the overproduction can be observed during the entire term of pregnancy, in the horse the overproduction is manifest mainly during the first third of the pregnancy; and whereas the woman eliminates large quantities of hormones with the urine, the horse, although having a high hormonal content in the blood, eliminates only small quantities in the urine. Examinations on the hypophysis of pregnant horses have not been made as yet. Tests on full term placentas from horses revealed a high content in folliculin but no hypophyseal hormones. The author emphasizes that, in biologic tests, generalizations should be made with discrimination. In the horse, for instance, the hormonal conditions during pregnancy differ considerably from those that are found in cows and hogs, although the placenta formation is the same in these three species. The author considers the question whether the placenta produces or only stores the hypophyseal hormone of minor importance. In investigations on minor problems, the great significance of the anterior lobe of the hypophysis for the sexual functions should not be lost sight of. Without the anterior lobe of the hypophysis and its hormones there would be no sexual function or rhythm, no maturation of the ovum, atrophy of the genitalia and no conception. If the anterior lobe is destroyed, the fertilized ovum dies.

On the mechanism of the inhibition of gastric secretion by fat. The role of bile and cystokinin. Kosaka, T. and R. K. S. Lim, Chinese J. Physiol. **4**: 213. 1930.

Studies were made on 2 dogs with Haidenhain pouches. It was found that bile is not the humoral inhibitory agent in fat inhibition of gastric secretion. A sample lot of Ivy's cystokinin caused definite inhibition of gastric secretion to a meal when injected intravenously in doses of about 5 mgm. per kgm. This suggests that cystokinin may include or may actually be the chalone for gastric secretion.—R. G. H.

Hyperinsulinism from B-cell adenoma of pancreas. Carr, A. D., R. Parker, E. Grove, A. O. Fisher and J. W. Larimore, J. A. M. A. **96**: 1363. 1931. Abst., A. M. A.

The authors report the case of a youth of 19, who suffered increasingly of attacks that were similar to the syndrome resulting from an overdose of insulin. They were relieved by the ingestion or administration of dextrose. The increasing severity of the attacks justified exploration and caused the patient and his parents to accept surgical measures. A localized tumor of the pancreas was found and removed. It showed chiefly B-cells. The postoperative recovery was prompt and uneventful and the clinical cure was complete and was confirmed by studies of the blood sugar.

The action of bile acids in diabetes (Über den Einfluss peroral zugeführter Gallensäuren auf den Zuckerstoffwechsel des Diabetischen). Horsters, H. and H. Rothmann, Arch. f. exper. Path. u. Pharmakol. **142**: 261. 1929. Abst., Physiol. Absts. **16**: 40.

Both the oral and intravenous administration of bile acids and their salts produced a fall in blood sugar in normal subjects and in diabetics, comparable to that produced by insulin. In diabetics bile acids diminish the increase in blood sugar which follows a meal. In mild cases of diabetes the carbohydrate tolerance is improved by bile acids, but in severe cases bile acids seem to produce no effect. It is suggested that the bile acids act by stimulating the pancreas to an increased production of insulin.

Distribution of insulin in body after injection (Insulinverteilung im Organismus nach Insulininjection. I. Mitteilung. II. Mitteilung: Abhängigkeit von Ernährungsweise und Blutzuckergehalt). Horster, H., Arch. f. exper. Path. u. Pharmakol. **153**: 214. 1930. Abst., Physiol. Absts. **16**: 46.

The author has attempted to determine the distribution of insulin in the body of a rabbit after injection. He has estimated the insulin in an organ by making an extract with Tyrode solution, and injecting this into 3 mice, and

determining their blood sugar after a given interval. By reference to a curve relating the fall in sugar percentage to the amount of insulin injected into the mice, he estimates the amount of insulin present in the organ extract.

The hyperglycemic power of the blood from a depancreatized dog is not changed by a previous injection of insulin (Le pouvoir hyperglycémiant du sang de chien dépancréaté n'est pas modifié par une injection préalable d'insuline). Kepinov, L. and S. Petit-Dutaillis, Compt. rend. Soc. de biol. **103**: 1190. 1930.

The test animal was a depancreatized dog carrying a pancreatic graft just large enough to maintain his blood sugar at a normal level. Blood from a normal dog transfused into the test animal did not affect his blood sugar level. Blood from a diabetic dog produced a marked and prolonged rise of blood sugar. If the diabetic dog received insulin and his blood was taken when his blood sugar had fallen to normal, it still produced an active hyperglycemia in the test animal.—J. C. D.

Relation between insulin and adrenalin in man (Über die Beziehungen zwischen Insulin und Adrenalin im menschlichen Organismus). Kugelmann, B., Klin. Wchnschr. **10**: 59. 1931. Abst., Physiol. Absts. **16**: 118.

The experiments were carried out mostly on healthy men, but in some instances on hospital patients. Thirty minutes after the intravenous injection of 30 units of insulin the blood sugar falls. When it has reached 60 mgm.% the blood pressure rises considerably. If glucose be given with the insulin the blood pressure does not rise. When the systolic blood pressure rises the diastolic pressure falls. The author attributes these results to the secretion of adrenalin in response to the fall in blood sugar, and states that the symptoms of hypoglycaemia are due to the outpouring of adrenalin. In support of the view that the rise in blood pressure is due to adrenalin it was found (1) in patients with enlarged spleens that the latter diminished greatly in size after injection of insulin, and (2) associated with the blood pressure rise a marked lymphocytosis and leucocytosis were found.

Hypoglycemia associated with hypertrophy of islands of Langerhans. Phillips, A. W., J. A. M. A. **96**: 1195. 1931. Abst., A. M. A.

According to Phillips, hypoglycemia appears to be due primarily to pathologic changes in the liver, endocrine glands or pancreas, and is seen in various diverse conditions. A case is presented which clinically appeared to be uremia with low blood sugar estimations. Autopsy showed hypertrophy of the islands of Langerhans and nephritic changes. It would seem that hypertrophy of the islands of Langerhans may be a cause for hyperinsulinism and hypoglycemia.

Experiences with a high carbohydrate-low calorie diet for the treatment of diabetes mellitus. Rabinowitch, I. M., Canad. M. A. J. **23**: 489. 1930.

Excellent results are claimed for a diet consisting of only 50 to 55 grams of fat, fruits and vegetables, and bread to make up the calorie requirements. The diet is an undernutrition one in the sense that diabetics are kept 5 to 10 pounds under weight, but sufficient food is given for comfort and daily duties. In many cases insulin becomes unnecessary on this diet. Full dietary details are given in the original paper.—A. T. C.

Angina pectoris and diabetes mellitus. Root, H. F. and A. Graybiel, J. A. M. A. **96**: 925. 1931. Abst., A. M. A.

Two hundred and ten cases of angina complicating diabetes mellitus are reviewed by the authors. The incidence of angina in patients with diabetes mellitus is extraordinarily high. The nearly equal sex ratio suggests the leveling influence of the associated diabetes. The occurrence of angina in the young, the long duration of diabetes before the onset of angina, and the late age of onset of angina, all point to the complicating diabetes as the factor that makes this group differ from the nondiabetic series. The prognosis for life is shorter than in the nondiabetic series, but should improve with modern dietary and insulin treatment. Diabetes mellitus with its associated coronary disease is a frequent contributing factor in the production of angina and, like syphilis, its presence should be investigated by special methods, such as blood sugar analyses.

Diabetes and pernicious anemia. Root, H. F., J. A. M. A. **96**: 928. 1931. Abst., A. M. A.

A series of 48 cases of combined diabetes mellitus and pernicious anemia, including 7 autopsies, were studied by the author. The symptoms of diabetes preceded the symptoms of anemia in the great majority of cases. Factors predisposing to a more frequent combination of the two diseases are the greater duration of life brought about by improved treatment of each disease and greater interest in diagnosis: Achlorhydria, which is frequent in diabetes and becomes more frequent with increasing age, may be an etiologic factor. Gastric analysis and examination of the blood for evidences of anemia should be performed on all diabetic patients and particularly searched for in cases of long duration. Treatment by means of insulin, liver or a potent substitute, and a diet rich in vitamins gives good results.

Effects of different modes of administration of insulin (Über die Wirkung des Insulins in Abhängigkeit von der Anwendungsmethode). Schmidt, A. A., Ztschr. f. d. ges. exper. Med. **73**: 599. 1930. Abst., Physiol. Absts. **16**: 117.

The intravenous injection of a single dose of 3 units of insulin per kilo in rabbits produced an ephemeral hypoglycaemic reaction, only 1 out of 15 showing convulsions. A similar injection subcutaneously produced an intense hypoglycaemic reaction, which in the vast majority of cases was accompanied by convulsions. Convulsions were much more frequently produced, when the intravenous method was used, if the same dose was given in repeated smaller injections. It is considered that insulin injected intravenously is rapidly removed from the circulation by the tissues and inactivated.

Carbohydrate metabolism in hypertension. Wishnofsky, M. and C. S. Byron, Arch. Int. Med. **47**: 790. 1931.

A dextrose tolerance test was performed on ten patients suffering from hypertension. The blood sugar and the respiratory quotient curves were studied simultaneously. In 6 of the 10 cases the blood sugar during fasting was higher than normal. It was shown that all patients with hypertension have high blood sugar curves. The respiratory quotient curves were normal in 9 of the 10 cases. This is adequate proof that there is no diminution in the secretion of insulin in hypertension, and that these patients are neither potentially nor mildly diabetic. It disproves the theory that the disturbance in carbohydrate metabolism in hypertension is caused by sclerosis of the blood vessels of the pancreas. In the case in which the respiratory quotient curve was lower than normal, diabetes mellitus, independent of the hypertension, could be considered to exist. The theory that hyperadrenalinemia is the cause of the disturbance cannot be proved in the present state of knowledge. The mechanism concerned in producing this disturbance in carbohydrate metabolism in hypertension is unknown and awaits further research for its elucidation.—Authors' Summary.

Secretin and blood sugar content (Über den Einfluss des Sekretins auf den Blutzuckergehalt). Yasuda, M., J. Biochem. **11**: 479. 1930. Abst., Physiol. Absts. **16**: 49.

Drugs affecting the nervous system cause hyperglycaemia and hypophosphataemia, but after injection of secretin there is both hyperglycaemia and hyperphosphataemia. The effect of adrenaline upon blood sugar and phosphates can be suppressed by the simultaneous use of secretin.

Relations between the external and internal secretions of the pancreas (Relations entre les sécrétions externe et interne du pancréas). Zunz, M. and J. La Barre, Bull. Acad. roy. de méd. de Belgique, **8**: 801. 1928. Abst., Rev. belge sc. med. **3**: 101.

The authors show that the intravenous injection of non-hypotonic secretin causes a progressive decrease of glycemia. The intravenous injection of non-hypotonic secretin does not cause an increase of insulin secretion. This effect is observed even after sub-cardiac section of the pneumogastric nerves. These facts indicate that there is a parallelism between the exocrine and endocrine secretion of the pancreas.—J. Gagnon.

Calcium, parathyroidectomy, and the vasomotor reflex of the carotid sinus in dogs (Calcium, parathyroïdectomie et réflexes vasomoteurs du sinus carotidien chez la chien). Bouckaert, J. J. and P. Regniers, Compt. rend. Soc. de biol. **103**: 920. 1930.

The reflex is not modified for the first 3 hours after operation. When tetanic spasms are about to appear, the reflex has disappeared and can not be restored by injections of calcium.—J. C. D.

Action of ergosterol in parathyroid deficiency (Azione e meccanismo d'azione di dosi eccessive d'ergosterolo irradiato sull'insufficienza paratiroidea sperimentale). Comel, M., Arch. di fisiol. **29**: 123. 1930. Abst., Physiol. Absts. **16**: 57.

Large doses of irradiated ergosterol given to dogs per os or subcutaneously before or after parathyroidectomy prevented the appearance of the usual symptoms of parathyroid deficiency. The ergosterol caused an increase in the quantity of calcium in the blood, but this was not sufficient to prevent slight hypocalcemia after removal of the parathyroids. However, the increase of phosphorus in the blood was less than usual, so that the Ca/P ratio remained greater than unity. After a few days the quantities of phosphorus and calcium in the blood returned to normal and the animals survived indefinitely.

The effect of Collip's parathormone on the chronaxie, the plethysmographic curve and blood calcium in man (Action des injections de parathormone de Collip sur la chronaxie, la courbe pléthysmographique et la calcémie chez l'Homme). Marinesco, G., C. I. Parhon and A. Kreindler, Compt. rend. Soc. de biol. **103**: 1040. 1930.

Two normal subjects were given parathormone injections every 6 hours. The chronaxie was increased. There was muscular vasoconstriction followed rapidly by vaso-dilation on voluntary muscular exercise. Calcium increased 15 to 25%. These results suggest vegetative changes similar to those found in myasthenia.—J. C. D.

Combined action of thyroxin and anterior hypophysis extract on guinea pigs thyroid (Action combinée de la thyroxine et de l'extrait préhypophysaire sur la thyroïde chez le Cobaye). Aron, M., Compt. rend. Soc. de biol. **104**: 96. 1930.

The former reduces the size of the gland when given alone, while the latter increases it. Given in proper proportion, they neutralize one another and the size of the gland is unaffected.—J. C. D.

Does the thyroid take part in the changes of the ovary and genital tract of immature rats subject to injections of urine from pregnant women (La thyroïde intervient-elle dans les modifications de l'ovaire et du tractus génital du rat prébubère sous l'action d'injections d'urine de femme gravide)? Bourg, R., Compt. rend. Soc. de biol. **104**: 105. 1930.

Young rats were thyroidectomized. One group of these received implantations of guinea pig hypophysis. Both groups received 5 injections of urine from a woman in the first half of pregnancy. The reactions of both groups resembled that given by unoperated animals. The thyroid, therefore, does not take an essential part in this reaction.—J. C. D.

The inhibitory influence of the thyroid gland on gastric secretory activity. Chang, H. C., Chinese J. Physiol. **4**: 247. 1930.

The effect of thyroidectomy on the gastric secretion of 2 dogs was studied. The change, consisting of a marked exaggeration of the fluctuations of both the basal and meal secretion, appeared on the third or fourth day and continued as long as the animals lived (106 days longest period observed). Whereas the basal secretion on certain days was normal in value, the meal response was almost invariably raised above the normal. The mechanism of the thyroid effect is now under investigation. The results, however, suggest that gastric secretory activity may be inversely related to that of the thyroid in the normal animal.—R. G. H.

The problem of the iodine treatment of hyperthyroidism (Problem Jodovenho Leceni Hyperthreos). Charvat, J., Casap. lék. česh. **70:** 13. 1931.

From the author's personal studies in Czechoslovakia and study of the literature of other countries it is concluded that the thyroid cell is able to secrete either colloid into the vesicles, or thyroxin directly into the circulation. If the formation of thyroxin falls, colloid begins to be stored. If the output of thyroxin rises, the storage of colloid ceases and, if the secretion continues to rise, the colloid finally disappears from the vesicles. Colloid should not be regarded as only a deposit of biologically active iodine. Iodine, in small doses, provokes greater storage of colloid and that more easily as the gland is poorer in colloid. With small doses of iodine in exophthalmic goiter storage of colloid begins, and the output of thyroxin is simultaneously reduced; the exophthalmic goiter becomes transformed into colloid goiter, the hyperfunctional stage passes into a resting stage. Large doses of iodine have a toxic action on the cells, the more easily as the gland is of less functional value. More or less serious injury to the cells may be caused, with a sudden flooding of colloid into the circulation followed by clinical signs of hyperthyroidism. Therefore, the problem of iodine treatment of goiters, and of exophthalmic goiter especially, becomes a problem of dosage. In seaside territories, where there is a sufficient quantity of iodine in the soil, water and food, exophthalmic goiter bears, and perhaps even demands, much larger doses of iodine than in countries where endemic goiter is common. Adenoma is the expression of an attempt of the thyroid to enlarge in some way its functioning parenchyma. It generally originates in colloid goiter, and, properly speaking, is a certain sign of functional inferiority of the remaining gland. As long as it does not undergo a secondary degeneration, it is able to function independently of the remaining glandular tissue, and may therefore of itself lead to hyperthyroidism. In adenoma a hyperplastic tissue, similar to that in exophthalmic goiter, may be found, whereas the remaining parenchyma may be colloid, or, on the whole, in a stage of functional inferiority. If therefore we treat a toxic adenoma by iodine, we never know whether a beneficial action on hyperplastic adenomatous tissue will appear, or whether a noxious influence on the remaining inferior parenchyma will predominate. In countries where there are no goitrogenous factors and where endemic goiter does not virtually appear, iodine will act successfully, since, above all, its beneficial action on the hyperplastic adenomatous tissue will take place. In such places, however, where endemic goiter is more often found, and where, therefore, the thyroid cells are functionally weaker, the noxious influence of iodine on the non-adenomatous parenchyma will easily predominate. The various sensibility of goiters, conditioned geographically, may lead to contradictory results, which, having been applied in another environment, might occasion considerable damage.—Author's Abst. (abbreviated).

Pregnancy complicating hyperthyroidism and following thyroidectomy. Fahrni, G. S., Canad. M. A. J. **23:** 645. 1930.

Fahrni considers that when pregnancy and hyperthyroidism co-exist, if the patient is less than 5 months pregnant, a thyroidectomy is the preferable procedure. The risk to the patient is not much increased by pregnancy, and there seems to be little danger of miscarriage. The interruption of pregnancy at 3 to 5 months is more dangerous than a properly conducted thyroidectomy. After operation the pregnant woman is able to go through to confinement in a comparatively normal manner. In women 6 to 9 months pregnant he favors conservative treatment, with operation not too soon after confinement. Subsequent to thyroidectomy he favors advice against pregnancy for at least two years, but should pregnancy occur in this interval there is as a rule no justification for advising interruption of pregnancy. He stresses particularly the absence of congenital deformities in babies born under such conditions.

—A. T. C.

Studies of exophthalmic goiter and involuntary nervous system. Hyman, H. T., and L. Kessel, J. A. M. A. **96:** 2014. 1931. Abst., A. M. A.

The authors classify patients afflicted with disturbances of the thyroid gland or of the involuntary nervous system in 3 groups: (1) those with morphologic changes in the thyroid gland (simple goiter) but without sympathomimetic symptoms (autonomic imbalance) or elevation of the basal metabolic rate; (2) those with sympathomimetic symptoms (autonomic imbalance) but without elevation of the basal metabolic rate and with or without goiter; (3) those with autonomic imbalance goiter and definite and sustained eleva-

tion of the basal metabolic rate (exophthalmic goiter, the Graves syndrome and Basedow's disease). All patients with simple goiter, cysts or adenomas of the thyroid gland should receive iodides. The drug may be administered as the saturated solution of sodium iodide in doses of from 0.2 to 0.5 cc. daily. The salt can be added to soup or any other liquid vehicle. It should be given daily, except on Sunday, for from two to four weeks before a second examination is made. Patients with "goiterophobia" should also be given bromides or other sedatives. The patient with uncomplicated simple goiter should receive reassurance that he is no more a candidate for exophthalmic goiter than his nongoitrous neighbor, that pressure symptoms are infrequent, that the goiter is benign and that complications are rare. Within the month the gland should be re-examined. This provides ample time for the complete conversion of the hyperplasia into the colloidal stage. Whether or not the goiter responds, maintenance doses of iodide two days in the week are continued for at least a year, with the object of preventing secondary hyperplasia. Double doses are employed during pregnancy and menses. Prophylactic dosage to female children of the family is also prescribed. The promiscuous and uncontrolled use of iodized foods is inadvisable. Iodide therapy, both curative and prophylactic, should be controlled medically. In simple goiter there are four medical indications for operative intervention: (a) suspicion of malignancy; (b) objective signs in the trachea or larynx indicating pressure; (c) frequent thyroid apoplexy from intracapsular rupture of a brittle and thickened vessel, and (d) marked deformity from an unsightly goiter. The clinical management of patients with autonomic imbalance is exceedingly difficult and frequently disappointing. Whether or not the imbalance is accompanied by goiter, iodides may be exhibited and at times seem to exert as specific an effect as in true exophthalmic goiter. Ergotamine tartrate specifically depresses the thoracolumbar system and doses of from 0.001 to 0.004 gm. 3 times daily may be tried. Rarely have the authors obtained a noteworthy or clearly defined clinical result. The use of endocrine products is also disappointing. Foci of infection should be eradicated. Excellent results may be obtained through psychotherapy, though no particular technic is required to study or treat these patients. A careful inquiry into the patient's routine, his ambitions and frustrations will yield a treasure trove of information. Fatigue is a common exciting factor. Therapy consists primarily in pointing out the relationship between symptoms and the psychic trauma and reassurance that the symptoms are not evidences of any organic disease or even harbingers thereof. The obvious psychic trauma is eliminated, if possible. Otherwise, the patient is advised to accept his burden and bear his cross. A word to relatives, friends or business associates is frequently helpful. Relaxation and rest are prescribed. Bromides and hypnotics are very useful symptomatically. Spending Sunday or the week-end in bed frequently stabilizes the nervous system. A vacation may be followed by complete relief of symptoms, but in all instances patients must be warned that recurrence of the "reaction picture" will follow provocation. When the budget permits, a complete rest cure of the Weir Mitchell type may be rewarded by a gratifying result. In a few instances, the psychic trauma is not readily revealed, and more elaborate psychiatric methods, particularly psychoanalysis, are indicated. The patient with exophthalmic goiter should be institutionalized and a careful physical examination and investigation of the psychic status made. High calory feeding, sedatives and hydrotherapy are prescribed. Foci of infection are sought for and, if possible, eradicated as soon as the general condition of the patient permits. A very intimate transference between the patient and the physician is attempted. In difficult or obscure psychic conditions, the aid of a trained psychiatrist is sought, but the need is rare. Sodium iodide is immediately administered as a saturated solution from 0.2 to 0.5 cc. three times a day. Although some patients continue to present symptoms or even grow worse while in the uphill phase of the disease, the iodides are not responsible for the persistence or exacerbations of the symptoms. There are no contraindications for their use. In approximately 50% of instances, more often in the younger than in the older group, striking, almost specific, improvement will occur. The morphology of the gland (adenoma) in no way modifies the response. When the effect of the iodide has reached its fastigium, surgical intervention is indicated in the following groups: (1) patients over the age of 35; (2) in the presence of pressure symptoms corroborated by roentgen or laryngoscopic observations; (3) when the galnd suggests a malignant degeneration; (4) all patients with organic damage, as indicated by persistent hypertension, cardiac irregularity, alterations in the functioning of the liver or in the pigmentation of the skin; (5) two or more exacerbations of the disease,

despite adequate conservative treatment; (6) all patients, young or old, who must necessarily be returned to a life of social or economic stress, or who are unable perfectly to adjust themselves to their problems, and (7) when the goiter is unsightly and regarded by the patient as a symboi of the disease.

The "thyroid heart" with low basal metabolic rate. Morris, R. S., Am. J. M. Sc. **181**: 297. 1931.

The author believes that too much emphasis has been placed on the basal metabolic rate in the etiology of chronic heart disease. When there is any evidence of a thyrotoxic state, either past or present, a subtotal thyroidectomy should be performed even if the basal metabolism is subnormal. When adenomata of the thyroid are present, they should be removed before any cardiac symptoms are produced.—E. L.

Site of action of thyroid in metabolism (Zur Frage des Angriffspunktes der stoffwechselsteigernden Schilddrüsenwirkung). Riml, O. and H. G. Wolff, Arch. f. exper. Path. u. Pharmakol. **157**: 178. 1930. Abst., Physiol. Absts. **16**: 125.

Extirpation of the stellate ganglia, or section of the splanchnics, or the splanchnics and the abdominal vagi, or splanchnic section combined with denervation of the extremities has no influence on the increase of metabolism following the administration of dried thyroid gland. The action of thyroid is therefore very probably peripheral.

Basal metabolism after thyroxin in sympathectomized animals. Ring, G. C., S. Dworkin and Z. M. Bacq, Am. J. Physiol. **97**: 315. 1931.

Removal of the thoraco-lumbar sympathetic chains in cats did not prevent the usual rise in metabolism after thyroxin.—R. G. H.

Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter. Thompson, W. O., A. E. Morris, and P. K. Thompson, Arch. Int. Med. **46**: 946. 1930.

Of 190 cases of exophthalmic goiter in which the patients underwent subtotal thyroidectomy during the years 1923 to 1928 at the Massachusetts General Hospital and which were followed for from three months to nearly six years after operation with frequent physical examinations and tests of basal metabolism, 37, or 19.5 per cent, showed definite clinical evidence of postoperative thyrotoxicosis with basal metabolic rates ranging from plus 19 to plus 63 per cent without medication. In only two instances was there evidence that it was a true recurrence rather than a persistence of the disease. In three cases, however, regeneration of thyroid tissue was observed in association with a persistence. This condition was sometimes noted in spite of the administration of iodine and repeated subtotal thyroidectomies. The postoperative thyrotoxicosis lasted from about two to four years in the three cases in which it finally disappeared without further surgical measures or roentgen treatment. It lasted for at least one year in 19 others and at least from four to six years in four others. The degree of thyrotoxicosis was usually not severe; with a single exception it was less than before operation. All of the patients resumed their customary occupation, although under a definite handicap in the instances in which the diseases persisted in moderately severe and in severe form. In 18 cases the basal metabolism could be held at a constant level for from months to years by the prolonged administration of iodine. In 10 cases in which iodine was ineffective, or eventually became so, or in which it did not abolish the thyrotoxicosis completely enough, reoperation was recommended. In 7 cases roentgen therapy was tried, with fair results in 5 instances. From a preoperative standpoint, there was no definite distinguishing mark between those patients who had thyrotoxicosis following operation and those who did not. There was a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of thyrotoxicosis. The surgeons who did the most radical thyroidectomies (synonymous in general with those who had the most experience) had definitely a smaller percentage of cases of postoperative thyrotoxicosis than did the surgeons who had less experience and who usually did less extensive thyroidectomies. In the cases of persistence of the disease, we noted no relapses except those caused by the omission of iodine, and no remissions except those caused by its administration and the disappearance of the disease.—Authors' Summary.

Influence upon personality of thyroid dysfunction especially in Graves' disease.
Wholey, C. C., Pennsylvania M. J. **34**: 291. 1931.

This paper is a brief summary of the relationship of thyroid dysfunction to individual personality, with special emphasis upon the constitutional makeup in Graves' disease. Graves' disease carries with it an involvement of the autonomic nervous system. This puts a peculiar stamp upon the character or personality of the individual which is discernible also at times other than periods of acute exacerbation of the syndrome. Graves' disease is not necessarily associated with thyroid hyperactivity; thyroid underfunction may likewise be significant of the existence of the Graves' mechanism. Deep seated personality trends, such as those of the manic-depressive, or the praecox, may be ushered into clinical activity by thyroid involvement, with or without an associated Graves' syndrome.—I. B.